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Induction of antigen-specific tumor immunity by genetic and cellular vaccines against MAGE: enhanced tumor protection by coexpression of granulocyte-macrophage colony-stimulating factor and B7-1. Bueler H; Mulligan RC
Howard Hughes Medical Institute, Children's Hospital, Boston, Massachusetts, USA.
Mol Med (UNITED STATES) Sep 1996, 2 (5) p545-55, ISSN 1076-1551 Journal Code: CG3
Contract/Grant No.: CA63399, CA, NCI
Languages: ENGLISH
Document type: JOURNAL ARTICLE

BACKGROUND: A number of tumors express antigens that are recognized by specific cytotoxic T cells. The normal host immune responses, however, are not usually sufficient to cause tumor rejection. Using appropriate immunization strategies, tumor-specific antigens may serve as targets against which tumor-destructive immune responses can be generated. MAGE-1 and %%%MAGE%%%-%%%3%%% are two clinically relevant antigens expressed in many human melanomas and other tumors, but not in normal tissues, except testis. Here, we have investigated whether DNA and cellular vaccines against MAGE-1 and %%%MAGE%%%-%%%3%%% can induce antigen-specific anti-tumor immunity and cause rejection of MAGE-expressing tumors. MATERIALS AND METHODS: Mice were immunized against MAGE-1 and %%%MAGE%%%- %%%3%%% by subcutaneous injection of genetically modified embryonic fibroblasts or intramuscular injection of purified DNA. Mice were injected with lethal doses of B16 melanoma cells expressing the corresponding MAGE antigens or the unrelated protein SIV tat, and tumor development and survival were monitored. RESULTS: Intramuscular expression of MAGE-1 and %%%MAGE%%%-%%%3%%% by plasmid DNA injection and subcutaneous immunization with syngeneic mouse embryonic fibroblasts transduced with recombinant retroviruses to express these antigens induced specific immunity against tumors expressing MAGE-1 and %%%MAGE%%%-%%%3%%%. Both CD4+ and CD8+ T cells were required for anti-tumor immunity. Coexpression of granulocyte-macrophage colony-stimulating factor (%%%GM%%%-%%%CSF%%%) or B7-1 significantly increased anti-tumor immunity in an antigen-specific manner and resulted in a considerable proportion of mice surviving lethal tumor challenge. CONCLUSIONS: Our results suggest that genetic and cellular vaccines against MAGE and other tumor antigens may be useful for the therapy of tumors expressing specific markers, and that %%%GM%%%-%%%CSF%%% and B7-1 are potent stimulators for the induction of antigen-specific tumor immunity.

STIC Use Only Accession Number: 229,782

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 ********************************** *
WELCOME TO THE U.S. PATENT TEXT
FILE      * ****************************
***
=> s 424/93.21/ccls

L1       120 424/93.21/CCLS

=> s l1 and (gmcsf or gm(w)csf)

        105 GMCSF
      42802 GM
       4014 CSF
       1142 GM(W)CSF
L2       23 L1 AND (GMCSF OR GM(W)CSF)

=> s l2 and mage

        196 MAGE
L3       1 L2 AND MAGE

=> d
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1. 5,759,535, Jun. 2, 1998, Immunotherapeutic strategies for the treatment of cancer; Edward P. Cohen, **424/93.21**; 435/69.1, 172.3, 320.1 [IMAGE AVAILABLE]

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=> d kwic
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US PAT NO: 5,759,535 [IMAGE AVAILABLE] L3: 1 of 1 US-CL-CURRENT: **424/93.21**; 435/69.1, 172.3, 320.1

SUMMARY:

BSUM(3)

Only . . . gene products (e.g., p53); reactivated embryonic gene products not expressed in adult tissues (e.g., P91A found in the P815 mastocytoma); **MAGE** 1 (found in melanomas and human breast tumors); tissue specific self-antigens expressed by tumors (e.g., tyrosinase); and a variety of. . .

SUMMARY:

BSUM(6)

Many . . . et al., Int. J. Cancer 53:471-477 [1993]); interferon-.alpha., (IFN-.alpha.)(Porgador, A., et al., Int. Immunol 150:1458-1570 [1993]); granulocyte-macrophage colony stimulating factor (**GM**-**CSF**) (Dranoff, G., et al., Proc. Nat. Acad. Sci. USA 90:3539-3543 [1993]) and several others.

SUMMARY:

BSUM(7)

Immunizations . . . Int. J. Cancer 53:471-477 (1993), Karp, et al., J. Immunol 150:896-908 (1993)), IFN-.alpha.(Porgador et al., J. Immunol 150:1458-1470 (1993)), or **GM**-**CSF** (Dranoff, et al., Proc. Natl. Acad. Sci. USA 90:3539-3543 (1993)), among others (Pardoll, et al., Curr. Opin. Immunol 4:619-623 (1992),. . .

DETDESC:

DETD(80)

Exemplary . . . (Blankenstein, et al. J. Exp. Med. 173: 1047-1052 [1991]); and interleukin-4 (Golvrobeck, P. T., et al. Science 254: 713-716 [1991]) **GM**-**CSF** (Dranoff, G., et al., Proc. Nat. Acad. Sci. USA 90:3539-3543 [1993]) or other cytokines capable of augmenting an anti-tumor response. . .

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=> d date
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L3: 1 of 1 TITLE: Immunotherapeutic strategies for the treatment of cancer US PAT NO: 5,759,535 DATE ISSUED: Jun. 2, 1998 [IMAGE AVAILABLE]
APPL-NO: 08/242,405 DATE FILED: May 13, 1994

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   (FILE 'USPAT' ENTERED AT 15:46:12 ON 06 AUG 1998)
L1       120 S 424/93.21/CCLS
L2        23 S L1 AND (GMCSF OR GM(W)CSF)
L3         1 S L2 AND MAGE

=> s l2 and melanoma

      3543 MELANOMA
L4       8 L2 AND MELANOMA

=> d his

   (FILE 'USPAT' ENTERED AT 15:46:12 ON 06 AUG 1998)
L1       120 S 424/93.21/CCLS
L2        23 S L1 AND (GMCSF OR GM(W)CSF)
L3         1 S L2 AND MAGE
L4         8 S L2 AND MELANOMA

=> d 1-8
```

1. 5,788,963, Aug. 4, 1998, Isolation and/or preservation of dendritic cells for prostate cancer immunotherapy; Gerald P. Murphy, et al., **424/93.21**, 185.1, 277.1 [IMAGE AVAILABLE]

2. 5,759,535, Jun. 2, 1998, Immunotherapeutic strategies for the treatment of cancer; Edward P. Cohen, **424/93.21**; 435/69.1, 172.3, 320.1 [IMAGE AVAILABLE]

3. 5,705,151, Jan. 6, 1998, Gene therapy for T cell regulation; Steve W. Dow, et al., **424/93.21**, 450; 435/7.2, 69.1, 172.3, 320.1; 514/44; 935/54, 55, 62, 71 [IMAGE AVAILABLE]

4. 5,702,702, Dec. 30, 1997, Modified cytotoxic tall cell line

and compositions and methods for manufacture and use thereof as therapeutic reagents for cancer; Daniela Santoli, et al., 424/93.71, 93.1, 93.2, **93.21**, 93.7, 534; 435/2, 366, 372, 372.3; 514/2, 9, 10, 885; 552/576, 577, 581 [IMAGE AVAILABLE]

5. 5,683,690, Nov. 4, 1997, Modified cytotoxic tall cell line and compositions and methods for manufacture and use thereof as therapeutic reagents for cancer; Daniela Santoli, et al., 424/93.71, 93.1, 93.2, **93.21**, 93.7, 534; 435/2, 372.3, 375 [IMAGE AVAILABLE]

6. 5,637,483, Jun. 10, 1997, Irradiated tumor cell vaccine engineered to express **GM**-**CSF**; Glenn Dranoff, et al., **424/93.21**; 435/320.1; 514/44; 935/57, 62, 71 [IMAGE AVAILABLE]

7. 5,571,797, Nov. 5, 1996, Method of inducing gene expression by ionizing radiation; Tsuneya Ohno, et al., 514/44; 424/1.11, 1.49, 1.61, 1.65, 1.69, 93.2, **93.21**, 450; 435/69.1, 69.5, 172.3, 320.1; 536/24.1; 935/6, 34, 59, 62 [IMAGE AVAILABLE]

8. 5,470,730, Nov. 28, 1995, Method for producing T.sub.H -independent cytotoxic T lymphocytes; Phillip D. Greenberg, et al., 435/172.3; **424/93.21**; 435/69.1, 69.52, 70.4, 252.3, 320.1 [IMAGE AVAILABLE]
=> d fro 6

US PAT NO: 5,637,483 [IMAGE AVAILABLE] L4: 6 of 8
DATE ISSUED: Jun. 10, 1997
TITLE: Irradiated tumor cell vaccine engineered to express **GM**-**CSF**
INVENTOR: Glenn Dranoff, Lexington, MA
Richard C. Mulligan, Lincoln, MA
Drew Pardoll, Baltimore, MD
ASSIGNEE: Whitehead Institute for Biomedical Research, Cambridge, MA (U.S. corp.)
Johns Hopkins University School of Medicine, Baltimore, MD (U.S. corp.)
APPL-NO: 08/265,554
DATE FILED: Jun. 23, 1994
REL-US-DATA: Continuation of Ser. No. 956,621, Oct. 5, 1992, abandoned, which is a continuation-in-part of Ser. No. 771,194, Oct. 4, 1991, abandoned.
INT-CL: [6] A61K 48/00; C12N 15/00
US-CL-ISSUED: 424/93.21; 435/320.1; 514/44; 935/57, 62, 71
US-CL-CURRENT: **424/93.21**; 435/320.1; 514/44; 935/57, 62, 71
SEARCH-FLD: 424/93.21, 93.1, 93.2; 514/44; 435/320.1, 240.1
REF-CITED:

U.S. PATENT DOCUMENTS

4,931,275	6/1990	Shinitzky et al.	424/88
5,078,996	1/1992	Conlon, III et al.	424/85.1
5,098,702	3/1992	Zimmerman et al.	424/85.21

FOREIGN PATENT DOCUMENTS

3 922 444	1/1991	Federal Republic of Germany
WO92/05262	4/1992	World Intellectual Property Organization
WO92/07573	5/1992	World Intellectual Property Organization

OTHER PUBLICATIONS

Oettgen & Old, "The History of Cancer Immunotherapy", Biologic Therapy of Cancer Devita et al., Eds. (J. Lippincott Co.) pp. 87-119 (1991). Asher, et al., "Murine Tumor Cells Transduced With the Gene for Tumor Necrosis Factor-.alpha.", J. Immunol. 146: 3227-3234 (1991). Havell, et al., "The Antitumor Function Of Tumor Necrosis Factor (TNF)", J. Exp. Med. 167: 1067-1085 (1988).
Gansbacher, et al., "Retroviral Vector-mediated .gamma.-Interferon Gene Transfer into Tumor Cells Generates Potent and Long Lasting Antitumor Immunity" Cancer Res 50:7820 Dec. 15, 1990.
Forni, et al., "Helper strategy in tumor immunology: Expansion of helper lymphocytes and utilization of helper lymphokines for experimental and clinical immunotherapy" Cancer and Met. Reviews 7: 289-309 (1988). Wantanabe, et al., "Exogenous expression of mouse interferon .gamma. cDNA in mouse neuroblastoma C1300 cells results in reduced tumorigenicity by augmented anti-tumor immunity", Proc. Natl. Acad. Sci. USA 86: 9456-9460 (1989).
Tepper, et al., "Murine Interleukin-4 Displays Potent Anti-Tumor Activity in Vivo", Cell 57: 503-512 (1989).
Fearon, et al., "Interleukin-2 Production by Tumor Cells Bypasses T Helper Function in the Generation of an Antitumor Response" Cell 60: 397-403 (1990).
Gansbacher, et al., "Interleukin 2 Gene Transfer into Tumor Cells Abrogates Tumorigenicity and Induces Protective Immunity" J. Exp. Med. 172: 1217-1224 (1990).
Blankenstein, et al., "Tumor suppression after Tumor Cell-targeted tumor Necrosis Factor .alpha. Gene Transfer", J. Exp. Med. 173: 1047-1052 (1991).
Teng, et al., "Long-term inhibition of tumor growth by tumor necrosis factor in the absence of cachexia or T-cell immunity" Proc. Natl. Acad. Sci. USA 88: 3535-3539 (1991).
Colombo, et al., "Granulocyte Colony-stimulating Factor Gene Transfer Suppresses Tumorigenicity of a Murine Adenocarcinoma In Vivo" J. Exp. Med. 173: 889-897 (1991).
Rollins & Sunday, "Suppression of Tumor Formation In Vivo by Expression of the JE Gene in Malignant Cells", Mol. Cell Bio., 11: 3125-3131 (1991).
Hock, et al., "Interleukin 7 Induces CD4.sup.+ T Cell-dependent Tumor Rejection", J. Exp. Med. 174: 1291-1298 (1991).
Golumbek, et al., "Treatment of Established Renal Cancer by Tumor Cells Engineered to Secrete Interleukin-4", Science 254: 713-716 (1991). Foley, E.J., "Antigenic Properties of Methylcholanthrene-induced Tumors in Mice of the Strain of Origin", Cancer Res. 13: 835-837 (1953). Klein, et al., "Demonstration of Resistance against Methylcholanthrene-induced Sarcomas in the Primary Autochthonous Host", Cancer Res. 20: 1561-1572 (1960).
Prehn & Main, "Immunity to Methylcholanthrene-Induced Sarcomas", J. Natl. Cancer Inst., 18: 769-778 (1957).
Revesz, Laszlo, "Detection of Antigenic Differences in Isologous Host-Tumor Systems by Pretreatment with Heavily Irradiated Tumor Cells", Cancer Res. 20: 443-451 (1960).
Korman, et al., Proc. Natl. Acad. Sci. USA, 84: 2150-2154 (1987). Clerici, et al., "Detection of Cytotoxic T Lymphocytes Specific For Synthetic Peptides of gp160 In HIV-Seropositive Individuals", J. Immunol. 146: 2214-2219 (1991).
Venet, et al., "Cytotoxic T. Lymphocyte Response Against Multiple Simian Immunodeficiency Virus .sup.A (SIV) Proteins in SIV-Infected Macaques", J. Immunol. 148: 2899-2908

(1992).
Hosmalin, et al., "Priming With T Helper Cell Epitope Peptides Enhances The Antibody Response To The Envelope Glycoprotein of HIV-1 In Primates", J. Immunol. 146: 1667-1673 (1991).
Armentano, et al., "Effect of Internal Viral Sequences on the Utility of Retroviral Vectors", J. Virol. 61: 1647-1650 (1987).
Sanger, et al., "DNA sequencing with chain-terminating inhibitors" Proc. Natl. Acad. Sci. USA 74: 5463-5467 (1977).
Yokota, et al., "Use of a cDNA expression vector for isolation of mouse interleukin 2 cDNA clones: Expression of T-cell growth-factor activity after transfection of monkey cells", Proc. Natl. Acad. Sci. USA 82: 68-72 (1985).
Lee, et al., "Isolation and characterization of a mouse interleukin cDNA clone that expresses B-cell stimulatory factor 1 activities and T-cell- and mast-cell-stimulating activities", Proc. Natl. Acad. Sci. USA 83: 2061-2065 (1986).
Campbell, et al., "Isolation, structure and expression of cDNA and genomic clones for murine eosinophil differentiation factor", Eur. J. Biochem. 174: 345-353 (1988).
Gough, et al., "Structure and expression of the mRNA for murine granulocyte-macrophage colony stimulating factor", The EMBO Journal 4: 645-653 (1985).
Horley, et al., "Molecular cloning of murine intercellular adhesion molecule (ICAM-1)", The EMBO Journal 8: 2889-2896 (1989). Yagita, et al., "Molecular Cloning of the Murine Homologue of CD2", J. Immunol. 140: 1321-1326 (1988).
Wang, et al., "Molecular Cloning of the Complementary DNA For Human Tumor Necrosis Factor", Science 228: 149-154 (1985).
Gearing, et al., "Production and assay of interleukin 2", Lymphokines and Interferons: a Practical Approach Clemens, et al., Eds. (IRL Press, Oxford) pp. 296-299 (1987).
Hu-Li, et al., "Derivation of a T Cell Line That Is Highly Responsive to IL-4 And Il-2 (CT.4R) And Of An IL-2 Hyporesponsive Mutant Of That Line (CT.4S)", J. Immunol. 142: 800-807 (1989).
Le, et al., "Tumor Necrosis Factor and Interleukin 1 Can Act as Essential Growth Factors in a Murine Plasmacytoma Line", Lymphokine Research 7: 99-106 (1988).
Dexter, et al., "Growth of Factor-Dependent Hemopoietic Precursor Cell Lines", J. Exp. Med. 152: 1036-1047 (1980).
Dahl & Degre, "A Micro Assay For Mouse And Human Interferon", Acta. Pathol. Microbiol. Immunol. Scand. 80: 863-870 (1972).
Oliff, et al., "Tumors Secreting Human TNF/Cachectin Induce Cachexia In Mice", Cell, 50: 555-563 (1987).
Hannum, et al., "Interleukin-1 receptor antagonist activity of an human interleukin-1 inhibitor", Nature 343: 336-340 (1990).
Takei, Fumio "Inhibition of Mixed Lymphocyte Response By A Rat Monoclonal Antibody To A Novel Murine Lymphocyte Activation Antigen (MALA-2)", J. Immunol. 134: 1403-1407 (1985).
Danos & Mulligan, "Safe and efficient generation of recombinant retroviruses with amphotropic and ecotropic host ranges", Proc. Natl. Acad. Sci. USA 85: 6460-6464 (1988).
Parker & Stark, "Regulation of Simian Virus 40 Transcription: Sensitive Analysis of the RNA Species Present Early in Infections by Virus or Viral DNA", J. Virol. 31: 360-369 (1979).
Southern & Berg, "Transformation of Mammalian Cells to Antibiotic Resistance with a Bacterial Gene Under control of the SV40 Early Region Promoter", J. Mol. Appl. Genet. 98: 503-517 (1975).
Southern, E.M., "Detection of Specific Sequences Among DNA Fragments Separated by Gel Electrophoresis", J. Mol. Biol., 98: 503-517 (1975). Cone, et al., "Regulated Expression of a Complete Human .beta.-Globin Gene Encoded by a Transmissible Retrovirus Vector", Mol. Cell Biol. 7: 887-897 (1987).
Feinberg & Vogelstein, "A Technique for Radiolabeling DNA Restriction Endonuclease Fragments to High Specific Activity", Anal. Biochem. 132: 6-13 (1983).
Fidler, Isaiah J., "Biological Behavior of Malignant Melanoma Cells Correlated to Their Survival in Vivo", Cancer Res. 35: 218-234 (1975). Berd, et al., "Treatment of Metastatic Melanoma With an Autologous Tumor-Cell Vaccine: Clinical and Immunologic Results in 64 Patients", J. Clin. Oncol. 8: 1858-1867 (1990).
Rosenberg, et al., "Use of Tumor-Infiltrating Lymphocytes and Interleukin-2 In the Immunotherapy of Patients with Metastatic Melanoma" N. Engl. J. Med. 146: 720-734 (1977).
Brattain, et al., "Establishment of Mouse Colonic Carcinoma Cell Lines with Different Metastatic Properties", Cancer Res. 40: 2142-2146 (1980).
DeLeo, et al., "Cell Surface Antigens of Chemically Induced Sarcomas of the Mouse", J. Med. Exp. 146: 720-734 (1977).
Murphy, et al., "A Murine Renal Cell Carcinoma", J. Natl. Cancer Inst. 50: 1013-1025 (1973).
Bertram, et al., "Establishment of a Cloned Line of Lewis Lung Carcinoma Cells Adapted to Cell Culture", Cancer Letters 11: 63-73 (1980). Morrissey, et al., "Granulocyte-Macrophage Colony-Stimulating Factor Augments The Primary Antibody REsponse By Enhancing the Function of Antigen-Presenting Cells". J. Immunol. 139: 1113-1119 (1987). Steinman, Ralph M., "The Dendritic Cell system And Its Role in Imunogenicity", Annu. Rev. Immunol. 9: 271-296 (1991).
Sarimento, et al., "IgG or IgM Monoclonal Antibodies Reactive with Different Determinants on the Molecular Complex Bearing LYT 2 Antigen Block T Cell-Mediated Cytolysis in the Absence of Complement", J. Immunol. 125: 2665-2672 (1980).
Heufler, et al., "Granulocyte/Macrophage Colony-Stimulating Factor and Interleukin 1 Mediate and Maturation of Murine Epidermal Langerhans Cells Into Potent Immunostimulatory Dendritic Cells", J. Exp. Med. 167: 700-705 (1988).
Koo, et al., "The NK-1(-) Mouse: A Model To Study Differentiation of Murine NK Cells", J. Immunol. 137: 3742-3747 (1986).
Inaba, et al., "Indentification of Proliferating Dendritic Cell Precursors in Mouse Blood", J. Exp. Med., 175: 1157-1167 (1992). Hoover, et al., "Prospectively Randomized Trial of Adjuvant Active-Specific Immunotherapy for Human Colorectal Cancer", Cancer 55: 1236-1243 (1885).
Witmer-Pack, et al., "Granulocyte/Macrophage Colony-Stimulating Factor Is Essential for the Viability and Function of Cultured Murine Epidermal Langerhans Cells", J. Exp. Med. 166: 1484-1498 (1987).
Gray & Goeddel, "cloning and expression of murine immune interferon cDNA", Proc. Natl. Acad. Sci. USA 80: 5842-5846 (1983).
Dialynas, et al., "Characterization of the Murine T. Cell Surface Molecule, Designated L3T4, Identified by Monoclonal Antibody GK1.5: Similarity of L3T4 to the Human LEU-3/T4".
Chiu, et al., "Multiple biological activities are expressed by a

mouse interleukin 6 cDNA clone isolated from bone marrow stromal cells", Proc. Natl. Acad. Sci. USA 85: 7099-7103 (1988).
Mulligan, Richard C., "Gene Transfer and Gene Therapy--Principles, Prospects, and Perspective", Etiology of Human Disease at the DNA Level ed. Lindsten and Pettersson Ravan Press, Ltd. 1991.
Russell, Stephen J., "Lymphokine gene therapy for cancer", Immunology Today 11: 196-200 (1990).
SA Rosenberg Immunology Today 9(2)58-62 1988.
Connor et al., Proc. Am. Assoc. Can. Res., 33:335, Abstract No. 1996 (1992).
Porgador et al., Nat Immun., 13:113-130 (1994).
Driscoll, J.S. "The Preclinical New Drug Research Program of the National Cancer Institute", Cancer Treatment Reports 68(1):63-76 (1984). DeVita, Vincent T. "Principles of Chemotherapy," Cancer: Principles & Practice of Oncology, Fourth Edition, DeVita et al. (ed.), J.P. Lippincott, Philadelphia (1993), pp. 276-292.
ART-UNIT: 184
PRIM-EXMR: Jacqueline M. Stone
ASST-EXMR: Dale Curtis Hogue, Jr.
LEGAL-REP: Albert P.Pennie & Edmonds Halluin

ABSTRACT:
A method of altering the specific, systemic immune response of an individual to a target antigen by the co-administration of a cytokine an adhesion or accessory molecule and the target antigen. The target antigen may be a tumor cell, a tumor cell antigen, an infectious agent or other foreign antigen, or other antigens to which an enhanced systemic immune response is desirable. Alternatively, the antigen may be a non-foreign antigen when a suppression of a systemic immune response is desired. The resulting systemic immune response is specific for the target antigen. 17 Claims, 23 Drawing Figures

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(FILE 'USPAT' ENTERED AT 15:46:12 ON 06 AUG 1998)
L1 120 S 424/93.21/CCLS
L2 23 S L1 AND (GMCSF OR GM(W)CSF)
L3 1 S L2 AND MAGE
L4 8 S L2 AND MELANOMA

=> s l2 not (l3 or l4)

L5 15 L2 NOT (L3 OR L4)

=> d 1-15

1. 5,766,585, Jun. 16, 1998, Systemic gene treatment of connective tissue diseases with IRAP-1; Christopher H. Evans, et al., **424/93.21**, 93.1, 93.2, 529, 534; 435/172.3, 320.1; 514/44; 935/23, 71 [IMAGE AVAILABLE]

2. 5,763,415, Jun. 9, 1998, Destruction of the epithelium of an exocrine gland in the prophylactic and therapeutic treatment of cancer; Saraswati Vaidyanathan Sukumar, 514/44; 424/93.1, **93.21**; 435/69.1, 172.3, 235.1, 325; 514/2 [IMAGE AVAILABLE]

3. 5,744,122, Apr. 28, 1998, Diagnosis and treatment of cancer having clonal macrophage involvement; Michael S. McGrath, et al., 424/9.2, **93.21**; 435/5, 6, 69.1, 91.2, 91.33, 325, 366, 372; 514/44 [IMAGE AVAILABLE]

4. 5,741,486, Apr. 21, 1998, Safe vectors for gene therapy; Vinay K. Pathak, et al., **424/93.21**, 93.2 [IMAGE AVAILABLE]

5. 5,736,387, Apr. 7, 1998, Envelope fusion vectors for use in gene delivery; Ralph W. Paul, et al., 435/320.1; **424/93.21**; 435/6, 69.5, 69.51, 69.52, 69.7, 91.2, 325; 514/44; 530/350, 387.1; 536/23.5, 24.31 [IMAGE AVAILABLE]

6. 5,710,037, Jan. 20, 1998, Retroviral vector particles; Elio F. Vanin, et al., 435/325; 424/93.2, **93.21**; 435/320.1, 363, 366, 372; 536/23.72, 24.1 [IMAGE AVAILABLE]

7. 5,707,865, Jan. 13, 1998, Retroviral vectors for expression in embryonic cells; Donald B. Kohn, et al., 435/325; 424/93.1, 93.2, **93.21**; 435/172.3, 235.1, 320.1, 352, 354; 514/44; 536/23.1, 24.1; 935/22, 32, 66, 70 [IMAGE AVAILABLE]

8. 5,698,443, Dec. 16, 1997, Tissue specific viral vectors; Daniel Robert Henderson, et al., 435/320.1; **424/93.21**; 435/172.3, 252.3; 514/2, 44 [IMAGE AVAILABLE]

9. 5,688,773, Nov. 18, 1997, Method of selectively destroying neoplastic cells; E. Antonio Chiocca, et al., 514/44; 424/93.1, **93.21**; 435/172.3, 320.1 [IMAGE AVAILABLE]

10. 5,679,342, Oct. 21, 1997, Hepatitis C virus infected cell systems; Michael Houghton, et al., **424/93.21**, 189.1, 228.1; 435/5, 69.3, 70.3, 235.1, 239, 372.2, 372.3 [IMAGE AVAILABLE]

11. 5,672,493, Sep. 30, 1997, De novo induction of cells exhibiting characteristics of macrophages utilizing feline sarcoma virus; Levy Kopelovich, 435/172.3; 424/93.2, **93.21**; 435/366 [IMAGE AVAILABLE]
12. 5,652,130, Jul. 29, 1997, Retroviral vectors expressing tumor necrosis factor (TNF); Michael Kriegler, et al., 435/172.3; 424/93.2, **93.21**; 435/320.1, 366, 372 [IMAGE AVAILABLE]

13. 5,635,399, Jun. 3, 1997, Retroviral vectors expressing cytokines; Michael Kriegler, et al., 435/320.1; 424/93.2, **93.21**; 435/172.3 [IMAGE AVAILABLE]

14. 5,591,625, Jan. 7, 1997, Transduced mesenchymal stem cells; Stanton L. Gerson, et al., 435/366; **424/93.21**, 93.7; 435/172.3, 320.1; 935/62, 70, 71 [IMAGE AVAILABLE]

15. 5,574,205, Nov. 12, 1996, Homologous recombination for universal donor cells and chimeric mammalian hosts; Raju Kucherlapati, et al., 800/2; 424/9.2, **93.21**; 435/172.3, 320.1; 800/DIG.1, DIG.2; 935/62, 111 [IMAGE AVAILABLE]

=> d ab 9

US PAT NO: 5,688,773 [IMAGE AVAILABLE] L5: 9 of 15

ABSTRACT:
A method for selectively killing nervous system and peripheral neoplastic cells is provided. Viral vectors are used to selectively express a cytochrome P450 gene in neoplastic cells, whose gene product targets the cells for selective killing, by rendering the cells sensitive to a chemotherapeutic agent.

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(FILE 'USPAT' ENTERED AT 15:46:12 ON 06 AUG 1998)
L1 120 S 424/93.21/CCLS
L2 23 S L1 AND (GMCSF OR GM(W)CSF)
L3 1 S L2 AND MAGE
L4 8 S L2 AND MELANOMA
L5 15 S L2 NOT (L3 OR L4)

=> s mage()3

196 MAGE
2304355 3
L6 21 MAGE(W)3

=> s l6(p)melanoma

3543 MELANOMA
L7 11 L6(P)MELANOMA

=> d kwic

US PAT NO: 5,783,567 [IMAGE AVAILABLE] L7: 1 of 11
SUMMARY:

BSUM(22)

TABLE 3

Tumor Antigens	
Cancer	Associated Antigen
Melanoma	BAGE 2-10
Breast/Ovarian	c-ERB2 (Her2/neu)
Burkitt's lymphoma/Hodgkin's lymphoma	EBNA-1
Burkitt's lymphoma/Hodgkin's lymphoma	EBNA-2
Burkitt's lymphoma/Hodgkin's lymphoma	EBNA-3. . . lymphoma/Hodgkin's lymphoma EBNA-4
Burkitt's lymphoma/Hodgkin's lymphoma	EBNA-6
Burkitt's lymphoma/Hodgkin's lymphoma	EBV
Burkitt's lymphoma/Hodgkin's lymphoma	EBV LMP2A
Melanoma	GAGE-1
Melanoma	gp75
Cervical	HPV 16 E6
Cervical	HPV 16 E7
Cervical	HPV 18 E6
Cervical	HPV 18 E7
Melanoma	MAG
Melanoma	MAGE-1
Melanoma	MAGE-2
Melanoma	**MAGE**-**3**
Melanoma	MAGE-4b
Melanoma	MAGE-5
Melanoma	MAGE-6
Melanoma	MART-1/Melan-A
Pancreatic/Breast/Ovarian	MUC-1
Melanoma	MUM-1-B
Breast/Colorectal/Burkitt's lymphoma	p53
Melanoma	Pmel 17 (gp100)
Prostate	PSA Prostate Specific Antigen
Melanoma	Tyrosinase
	CEA Carcinoembryonic Antigen
	LRP Lung Resistance Protein
	Bc1-2
	Ki-67

=> s l7 and (gmcsf of gm()csf)

105 GMCSF
42802 GM
0 GMCSF OF GM
(GMCSF(1W)GM)
4014 CSF
0 GMCSF OF GM(W)CSF
L8 0 L7 AND (GMCSF OF GM(W)CSF)

=> s l7 and (gmcsf or gm()csf)

105 GMCSF
42802 GM
4014 CSF
1142 GM(W)CSF
L9 1 L7 AND (GMCSF OR GM(W)CSF)

=> d

1. 5,744,353, Apr. 28, 1998, Cytolytic T cell lines which bind to complexes of tumor rejection antigens and HLA-B44 molecules; Jean Herman, et al., 435/325, 372.3 [IMAGE AVAILABLE]

=> d date

L9: 1 of 1 TITLE:
Cytolytic T cell lines which bind to complexes of tumor rejection antigens and HLA-B44 molecules
US PAT NO: 5,744,353 DATE ISSUED: Apr. 28, 1998 [IMAGE AVAILABLE]
APPL-NO: 08/796,883 DATE FILED: Feb. 6, 1997 REL-US-DATA: Division of Ser. No. 602,506, Feb. 20, 1996, which is a continuation-in-part of Ser. No. 531,864, Sep. 21, 1995, which is a continuation-in-part of Ser. No. 373,636, Jan. 17, 1995, which is a continuation-in-part of Ser. No.

253,503, Jun. 3, 1994, Pat. No. 5,589,334.
=> d ab

US PAT NO: 5,744,353 [IMAGE AVAILABLE] L9: 1 of 1
ABSTRACT:
Tumor rejection antigens presented by HLA-B44 molecules are described. These peptides are useful in diagnostic and therapeutic methodologies. The tumor rejection antigens are derived from MAGE tumor rejection antigen precursors.

=> d his

(FILE 'USPAT' ENTERED AT 15:46:12 ON 06 AUG 1998)
L1 120 S 424/93.21/CCLS
L2 23 S L1 AND (GMCSF OR GM(W)CSF)
L3 1 S L2 AND MAGE
L4 8 S L2 AND MELANOMA
L5 15 S L2 NOT (L3 OR L4)
L6 21 S MAGE()3
L7 11 S L6(P)MELANOMA
L8 0 S L7 AND (GMCSF OF GM()CSF)
L9 1 S L7 AND (GMCSF OR GM()CSF)

=> s l7 not l9

L10 10 L7 NOT L9

=> d 1-10

1. 5,783,567, Jul. 21, 1998, Microparticles for delivery of nucleic acid; Mary Lynne Hedley, et al., 514/44; 435/320.1; 536/23.1 [IMAGE AVAILABLE]

2. 5,750,395, May 12, 1998, DNA encoding MAGE-1 C-terminal cytotoxic t lymphocyte immunogenic peptides; John D. Fikes, et al., 435/325, 69.3, 252.3, 254.2, 320.1; 536/23.5 [IMAGE AVAILABLE]

3. 5,695,994, Dec. 9, 1997, Isolated cytolytic T cells specific for complexes of MAGE related peptides and HLA molecules; Thierry Boon-Falleur, et al., 435/325, 355, 372.3; 530/328 [IMAGE AVAILABLE]
4. 5,662,907, Sep. 2, 1997, Induction of anti-tumor cytotoxic T lymphocytes in humans using synthetic peptide epitopes; Ralph T. Kubo, et al., 424/195.1, 193.1, 197.11, 277.1; 530/300, 328, 403 [IMAGE AVAILABLE]
5. 5,612,201, Mar. 18, 1997, Isolated nucleic acid molecules useful in determining expression of a tumor rejection antigen precursor; Etienne De Plaen, et al., 435/91.2, 6; 536/23.1, 24.33 [IMAGE AVAILABLE]
6. 5,591,430, Jan. 7, 1997, Isolated, MAGE-3 derived peptides which complex with HLA-A2 molecules and uses thereof; Alan Townsend, et al., 424/93.71, 185.1, 277.1; 435/7.24, 372.3; 530/328, 395, 828 [IMAGE AVAILABLE]

7. 5,541,104, Jul. 30, 1996, Monoclonal antibodies which bind to tumor rejection antigen precursor mage-1; Yao-Tseng Chen, et al., 435/344.1; 424/138.1, 155.1, 174.1; 435/69.6, 70.21, 172.2; 530/350, 387.7, 388.8; 935/15 [IMAGE AVAILABLE]

8. 5,512,444, Apr. 30, 1996, Method for determining bladder tumors by assaying for MAGE-1,2,3 or 4; Jean-Jacques Patard, et al., 435/6, 7.1, 7.9, 91.2; 536/23.1, 24.3 [IMAGE AVAILABLE]

9. 5,462,871, Oct. 31, 1995, Isolated nucleic acid molecules which encode MAGE derived nonapeptides; Thierry Boon-Falleur, et al., 435/354, 252.3, 365; 536/23.1, 23.5 [IMAGE AVAILABLE]

10. 5,342,774, Aug. 30, 1994, Nucleotide sequence encoding the tumor rejection antigen precursor, MAGE-1; Thierry Boon, et al., 435/371, 69.1, 69.3, 172.3, 235.1, 252.3, 320.1; 530/350; 536/23.5; 935/9, 32, 34, 57, 62, 70, 71 [IMAGE AVAILABLE]

=> d kwic

US PAT NO: 5,783,567 [IMAGE AVAILABLE] L10: 1 of 10
SUMMARY:

BSUM(22)

TABLE 3

Tumor Antigens	
Cancer	Associated Antigen
Melanoma	BAGE 2-10
Breast/Ovarian	c-ERB2 (Her2/neu)
Burkitt's lymphoma/Hodgkin's lymphoma	EBNA-1
Burkitt's lymphoma/Hodgkin's lymphoma	EBNA-2
Burkitt's lymphoma/Hodgkin's lymphoma	EBNA-3. . . lymphoma/Hodgkin's lymphoma EBNA-4
Burkitt's lymphoma/Hodgkin's lymphoma	EBNA-6
Burkitt's lymphoma/Hodgkin's lymphoma	EBV
Burkitt's lymphoma/Hodgkin's lymphoma	EBV LMP2A
Melanoma	GAGE-1
Melanoma	gp75
Cervical	HPV 16 E6
Cervical	HPV 16 E7
Cervical	HPV 18 E6
Cervical	HPV 18 E7
Melanoma	MAG
Melanoma	MAGE-1
Melanoma	MAGE-2
Melanoma	**MAGE**-**3**
Melanoma	MAGE-4b
Melanoma	MAGE-5
Melanoma	MAGE-6
Melanoma	MART-1/Melan-A
Pancreatic/Breast/Ovarian	MUC-1
Melanoma	MUM-1-B

Breast/Colorectal/Burkitt's lymphoma
p53
Melanoma Pmel 17 (gp100)
Prostate PSA Prostate Specific Antigen
Melanoma Tyrosinase
CEA Carcinoembryonic Antigen
LRP Lung Resistance Protein
Bc1-2
Ki-67

=> d kwic 2-10

US PAT NO: 5,750,395 [IMAGE AVAILABLE] L10: 2 of 10
SUMMARY:

BSUM(5)

More recently a new family of antigens has been described on **melanoma** tumors. These antigens, now termed the "**melanoma** antigen," or MAGE family of antigens, were identified in a **melanoma** cell line which was lysed by a panel of autologous cytotoxic T lymphocytes ("CTLs"). Cells which did not express a. . . any significant homology with any sequence in data banks, including GenBank. Two additional nonidentical cDNAs were also found (MAGE-2 and **MAGE**-**3**) which were more closely related to each other than to MAGE-1, but the three were approximately equally expressed.

US PAT NO: 5,695,994 [IMAGE AVAILABLE] L10: 3 of 10
DETDESC:

DETD(55)

As . . . gene and more than one MAGE antigen coding sequence. Given the finding that both a MAGE-1 derived nonapeptide and a **MAGE**-**3** derived nonapeptide are presented by a common HLA molecule supports this contention. Such cells may be regarded as universal effector. . . combined with a suitable adjuvant, such as those well known to the art. Treatment of various cancerous conditions, such as **melanoma** and breast cancer, may be carried out using these transfectant.

US PAT NO: 5,662,907 [IMAGE AVAILABLE] L10: 4 of 10
ABSTRACT:
The . . . treating cancer. The invention provides peptides based on a 9 residue epitope derived from the product of the tumor-associated gene **MAGE**-**3**. The peptide induces CTL that kill **melanoma** and other tumor cells lines.

SUMMARY:

BSUM(6)

In contrast with the somewhat limited frequency of expression of MAGE-1, the MAGE-2 and **MAGE**-**3** genes are expressed in approximately 80-90% of the **melanoma** lines examined, and also in the other tumor types such as breast, colon, lung and thyroid cancers (Zakut et al. (1990) Cancer Res. 53:5-8). Thus, it would be attractive to identify peptides derived from the MAGE-2 or **MAGE**-**3** gene products which could serve as CTL antigens.

SUMMARY:

BSUM(9)

The . . . a protein comprising an epitope having the sequence EVDPIGHLY (SEQ ID NO.:2). The cells are usually tumor cells, such as **melanoma** cells expressing a protein product of the **MAGE**-**3** gene. The peptides of the invention usually consist essentially of about 8 to about 10 residues and have the sequence. . .

DRAWING DESC:

DRWD(3)

FIGS. 2A and 2B show antigen-specificity and MHC-restriction analysis of **MAGE**-**3**-reactive CTL. FIG. 2A shows cytotoxic responses using peptide-loaded target cells and **melanoma** tumors: (.circle-solid.), Steinlin (HLA homozygous, Epstein-Barr Virus-transformed lymphoblastoid cell line, HLA-A1/1, -B8/8) pulsed with **MAGE**-**3** peptide EVDPIGHLY (SEQ ID NO.:2); (.tangle-solidup.), Steinlin cells pulsed with MAGE-1 peptide EADPTGHSY (SEQ ID NO.:1); (.largecircle.), Steinlin cells with no peptide; (.tangle-soliddn.), mel-397 (HLA-A1/25, **MAGE**-**3**+); (.DELTA.), mel-938 (HLA-A1/24, -B7/8, **MAGE**-**3**+); (.diamond.), mel-888 (HLA-A1/24, -B22/52, -Cw1/w7 **MAGE**-**3**-); (.diamond-solid.), mel-888 pulsed with **MAGE**-**3** peptide EVDPIGHLY (SEQ ID NO.:2); (.gradient.), mel-526 (HLA-A2/3, -B50/62, -Cw3, **MAGE**-**3**+). FIG. 2A demonstrates that CTLs induced with peptide EVDPIGHLY (SEQ ID NO.:2) can specifically kill **MAGE**-**3**-expressing **melanoma** tumor cells.

DRAWING DESC:

DRWD(5)

FIG. 3 shows cytotoxic activity of **MAGE**-**3**-specific CTL towards various tumors. The **MAGE**-**3** specific CTL was tested for its ability to kill breast and prostate HLA-A1+ tumor lines previously treated, or not, with .gamma.-IFN. Cytotoxic responses were measured against: (.circle-solid.), mel-397 **MAGE**-**3**+); (.largecircle.), mel-397 plus, .gamma.-IFN; (.box-solid.) HBL-100 (HLA-A1/10, -B7/8 **MAGE**-**3**+); (.quadrature.) HBL-100 plus .gamma.-IFN; (.tangle-solidup.), BT-20 (HLA-A1, -B16.**MAGE**-**3**+); (.DELTA.), BT-20 plus .gamma.-IFN; (.box-solid.), PC3 HLA-A1/9; (.diamond.), PC3 plus .gamma.-IFN; (.tangle-soliddn.) mel-888 plus .gamma.-IFN (**MAGE**-**3**.sup.-). FIG. 3 demonstrates that **MAGE**-**3**-specific CTL can kill tumors other than **melanoma** which express the **MAGE**-**3** gene product.

DETDESC:

DETD(4)

Synthetic peptides disclosed here can be used therapeutically to elicit CTL responses to **melanoma**, breast, colon, prostate, or other cells which express proteins (such as the **MAGE**-**3** or MAGE-2 gene products) having the EVDPIGHLY (SEQ ID NO.:2) epitope. This approach can be used therapeutically either in the. . .

DETDESC:

DETD(29)

The . . . to treat and/or prevent cancer. Examples of diseases which can be treated using the immunogenic peptides of the invention include **melanoma**, breast, colon, lung, and thyroid cancers. The expression of the **MAGE**-**3** gene can be determined using standard techniques such as measuring the presence of **MAGE**-**3** mRNA in the tumor cells, for example by PCR or Northern blot analysis.

DETDESC:

DETD(73)

Induction . . . the synthetic peptides. Out of the 6 peptides studied only one, the highest MHC binder (EVDPIGHLY (SEQ ID NO.:2)), from **MAGE**-**3** was able to elicit CTL in one of the blood donors. After 2 rounds of stimulation in culture with autologous. . . NO.:2), significant cytotoxic activity towards peptide-sensitized, HLA-A1-bearing target cells was observed (FIG. 2a). More significant was the observation that two **MAGE**-**3** -expressing HLA-A1 **melanoma** cell lines (397-mel and 938-mel, Zakut et al. (1990) Cancer Res. 53:5-8) were also killed by these CTL (FIG. 2a).. . .

DETDESC:

DETD(74)

Antigen Specificity and MHC Restriction Analysis. The CTL response appeared to be specific and HLA-A1-restricted, since HLA-A1 **melanoma** cells negative for **MAGE**-**3** (mel-888), and **melanoma** cells that expressed **MAGE**-**3**, but of a different HLA-A allelic type (mel-526, HLA-A2/A3 Zakut et al., supra) were not lysed by the CTL line. The exogenous addition of the peptide EVDPIGHLY to the **MAGE**-**3**- negative, HLA-Al-positive mel-888 cell line rendered the cells susceptible to lysis by the CTL (FIG. 2a, insert), indicating that this tumor. . .

DETDESC:

DETD(76)

Cytolytic Activity to Non-**Melanoma** Tumors. As mentioned above, other tumors besides melanomas can also express MAGE genes, in particular MAGE-2 and -3. The ability of the **MAGE**-**3**- specific CTL line to kill HLA-A1-expressing breast and prostate carcinoma cell lines was also tested. The results in FIG. 3 show that one of the two breast cancer cell lines (HBL-100), reported to express **MAGE**-**3** (Zakut et al., supra), was highly susceptible to lysis by the CTL. The level of lysis improved significantly if these. . . of MHC class I molecules on the cell surface. The other breast cancer cell line (BT-20), also reported to express **MAGE**-**3** (Zakut et al., supra), and the prostate cancer line (PC3) were also killed, but to a lesser extent, and only. . .

US PAT NO: 5,612,201 [IMAGE AVAILABLE] L10: 5 of 10

DETDESC:

DETD(133)

In . . . lymphocytes of the same patient. Also negative were several normal tissues of other individuals (FIG. 10 and FIG. 11). Fourteen **melanoma** cell lines of other patients were tested. Eleven were positive with bands of varying intensities. In addition to these culture cell lines, four samples of **melanoma** tumor tissue were analyzed. Two samples, including a metastasis of patient MZ2 proved positive, excluding the possibility that expression of. . . that showed complete specificity for one of the three genes (FIG. 9). Control experiments carried out by diluting RNA of **melanoma** MZ2-MEL 3.0 in RNA from negative cells indicated that under the conditions used herein the intensity of the signal decreased. . . expression of the three MAGE genes, suggesting therefore a level of expression of less than 1/300.sup.th that of the MZ2 **melanoma** cell line (FIG. 11). For the panel of **melanoma** cell lines, the results clearly showed that some melanomas expressed MAGE genes mage 1, 2 and 3 whereas other expressed. . . 10). Some of the other tumors also expressed all three genes whereas others expressed only mage-2 and 3 or only **mage**-**3**. It is impossible to exclude formally that some positive PCR results do not reflect the expression of one of the. . .

DETDESC:

DETD(179)

TABLE 3

	TNF pg/ml Exp 1	Exp 2
Melanoma	Number of Cells	+CTL 20/38	+CTL Expression 20/38 of **Mage**-**3** of HLA-A-1
MZ2-MEL.61.2	50000	1	4	+++	+
MZ2-MEL-ET1	50000	>120	>120	+++	+
	1666	66. . .			

DETDESC:

DETD(233)

The identification of **MAGE**-**3** derived TRAs as being presented by HLA-A1 molecules suggests various therapeutic and diagnostic approaches. In a therapeutic context, e.g., the treatment of a disorder characterized by **MAGE**-**3**

expression may be treated in a number of ways, "disorder" being used to refer to any pathological condition where **MAGE**-**3** TRAP is expressed, such as cancer (e.g., **melanoma**).
DETDESC:

DETD(237)

Adoptive . . . elaborated upon supra. The cells used in this approach may be those that normally express the complex, such as irradiated **melanoma** cells or cells transfected with one or both of the genes necessary for presentation of the complex. Chen et al.,. . . HLA molecule while the TRA is presented without the need for further processing. Thus, one may treat disorders where a **MAGE**-**3** derived TRA is presented by HLA-A1 molecules, or by any HLA molecule.
US PAT NO: 5,591,430 [IMAGE AVAILABLE] L10: 6 of 10
DETDESC:

DETD(50)

In addition, **melanoma** cell lines which were known to express **MAGE**-**3** and which were HLA-A2.sup.+ were used. These cell lines are identified in the figures as LB 373, LB43, LB24 clone. . .
US PAT NO: 5,541,104 [IMAGE AVAILABLE] L10: 7 of 10
DETDESC:

DETD(26)

Monoclonal . . . present in MZ2-MEL 3.1 lysate, but not in lysates of either of the other two cell lines. When three additional **melanoma** lines were tested, only those which were typed as being MAGE-1 positive reacted with the mAb. Expression of MAGE-2 or **MAGE**-**3** was irrelevant.

US PAT NO: 5,512,444 [IMAGE AVAILABLE] L10: 8 of 10
DETDESC:

DETD(16)

Table . . . (nomenclature is explained below). Of 57 samples of primary transitional cell carcinoma, 21% expressed MAGE-1, 30% expressed MAGE-2, 35% expressed **MAGE**-**3**, and 33% expressed MAGE-4. Ta tumors and low grade T1 tumors expressed none of these, or expressed only a single. . . invasive tumors studied. Among the 29 superficial tumors, the proportion was only 28%. Results paralleled other results reported previously for **melanoma**, in that all but one of the tumors expressing MAGE-1 also expressed **MAGE**-**3**.

US PAT NO: 5,462,871 [IMAGE AVAILABLE] L10: 9 of 10
DETDESC:

DETD(38)
. . .
TABLE 1

	TNF pg/ml Exp 1	TNF pg/ml Exp 2
Number of **Melanoma** cells -	+CTL Expression of **Mage** **3** HLA-A1 - 20/38	+CTL Expression of **Mage** **3** HLA-A1 - 20/38
MZ2-MEL-61.2		
	50000	1 4 +++ +
MZ2-MEL-ET1		
	50000	>120 >120 +++ +
	1666. . .	

DETDESC:

DETD(56)

As . . . gene and more than one MAGE antigen coding sequence. Given the finding that both a MAGE-1 derived nonapeptide and a **MAGE**-**3** derived nonapeptide are presented by a common HLA molecule supports this contention. Such cells may be regarded as universal effector. . . combined with a suitable adjuvant, such as those well known to the art. Treatment of various cancerous conditions, such as **melanoma** and breast cancer, may be carried out using these transfectants.
US PAT NO: 5,342,774 [IMAGE AVAILABLE] L10: 10 of 10
DETDESC:

DETD(103)

In . . . lymphocytes of the same patient. Also negative were several normal tissues of other individuals (FIG. 13 and FIG. 14). Fourteen **melanoma** cell lines of other patients were tested. Eleven were positive with bands of varying intensities. In addition to these culture cell lines, four samples of **melanoma** tumor tissue were analyzed. Two samples, including a metastasis of patient MZ2 proved positive, excluding the possibility that expression of. . . that showed complete specificity for one of the three genes (FIG. 12). Control experiments carried out by diluting RNA of **melanoma** MZ2-MEL 3.0 in RNA from negative cells indicated that under the conditions used herein the intensity of the signal decreased. . . expression of the three MAGE genes, suggesting therefore a level of expression of less than 1/300.sup.th that of the MZ2 **melanoma** cell line (FIG. 14). For the panel of **melanoma** cell lines, the results clearly showed that some melanomas expressed MAGE genes mage 1, 2 and 3 whereas other expressed. . . 1). Some of the other tumors also expressed all three genes whereas others expressed only mage-2 and 3 or only **mage**-**3**. It is impossible to exclude formally that some positive PCR results do not reflect the expression of one of the. . .

=> d his

(FILE 'USPAT' ENTERED AT 15:46:12 ON 06 AUG 1998)
L1 120 S 424/93.21/CCLS
L2 23 S L1 AND (GMCSF OR GM(W)CSF)
L3 1 S L2 AND MAGE
L4 8 S L2 AND MELANOMA
L5 15 S L2 NOT (L3 OR L4)
L6 21 S MAGE()3
L7 11 S L6(P)MELANOMA
L8 0 S L7 AND (GMCSF OF GM()CSF)
L9 1 S L7 AND (GMCSF OR GM()CSF)
L10 10 S L7 NOT L9

=> s (gmcsf or gm()csf)(p)(treatment)(p)(cancer or melanoma or malignancy or tumor or tumour)
105 GMCSF
42802 GM
4014 CSF
379440 TREATMENT
22994 CANCER
3543 MELANOMA
1994 MALIGNANCY
18528 TUMOR
1654 TUMOUR
L11 105 (GMCSF OR GM(W)CSF)(P)(TREATMENT)(P)(CANCER OR MELANOMA OR MAL
IGNANCY OR TUMOR OR TUMOUR)

=> d kwic

US PAT NO: 5,789,441 [IMAGE AVAILABLE] L11: 1 of 105
SUMMARY:

BSUM(39)

In . . . present invention, there is also provided the use of a LTB.sub.4 agent as an antiviral agent for the prophylaxis and **treatment** of viral infections in humans and animals in association with other agents including but not limited to granulocyte-macrophage colony-stimulating factor (**GM**-**CSF**), granulocyte colony stimulating factor (G-CSF), macrophage colony stimulating factor (M-CSF), interferons, **tumor** necrosis factor .alpha., interleukin-3 and interleukin-5, which have been shown to prime leukocytes for the synthesis of LTB.sub.4 or other. . .

=> d kwic 2

US PAT NO: 5,783,569 [IMAGE AVAILABLE] L11: 2 of 105
DETDESC:

DETD(26)

In . . . This property can be exploited in a therapeutic regimen for use as an adjuvant in parallel with radiation or chemotherapy **treatment**. Radiation and chemotherapy are known to result in neutropenia (reduced polymorphonuclear (PMN) leukocyte cell count) and thrombocytopenia (reduced platelet count). At present, these conditions are treated by the administration of colony-stimulating factors such as **GM**-**CSF** and granulocyte colony-stimulating factor (G-CSF). Such factors are effective in overcoming neutropenia, but fail to impact upon thrombocytopenia. Thus, the. . . minimize the development of thrombocytopenia which limits the dose of the radiation or chemotherapeutic agent which is used to treat **cancer**.

=> d kwic 3-105

US PAT NO: 5,776,095 [IMAGE AVAILABLE] L11: 3 of 105
DETDESC:

DETD(5)

A middle-age woman with advanced breast **cancer**, including bone and bone marrow invasion, has an aliquot of her bone marrow removed and harvested for regrafting after clearing the marrow of the **cancer** cells in vitro. The bone marrow in the patient is then destroyed by i.v. infusion of 20 mg NP-2 monoclonal antibody F(ab').sub.2 labeled with 200 mci Rhenium-188 according to the method of Griffiths et al. (**Cancer** Res. 51:4594, 1991). Approximately 3 weeks later, there is evidence of severe bone marrow toxicity which requires the infusion of the autologous bone marrow which was previously cleared of **cancer** cells, in combination with hematopoietic growth factor administration, in this case with **GM**-**CSF** given repeatedly before and after marrow grafting. Six weeks later, the patient has renewed bone marrow function and an MN3-Fab'. . . m) bone marrow scan shows good bone marrow imaging without evidence of metastatic defects. She is now a candidate for **treatment** of other sites of her metastatic breast **cancer**.

US PAT NO: 5,776,094 [IMAGE AVAILABLE] L11: 4 of 105
DETDESC:

DETD(5)

A middle-age woman with advanced breast **cancer**, including bone and bone marrow invasion, has an aliquot of her bone marrow removed and harvested for regrafting after clearing the marrow of the **cancer** cells in vitro. The bone marrow in the patient is then destroyed by i.v. infusion of 20 mg NP-2 monoclonal antibody F(ab').sub.2 labeled with 200 mCi Rhenium-188 according to the method of Griffiths et al. (**Cancer** Res. 51:4594, 1991). Approximately 3 weeks later, there is evidence of severe bone marrow toxicity which requires the infusion of the autologous bone marrow which was previously cleared of **cancer** cells,- in combination with hematopoietic growth factor administration, in this case with **GM**-**CSF** given repeatedly before and after marrow grafting. Six weeks later, the patient has renewed bone marrow function and an MN3-Fab'. . . (Tc-99m) bone marrow scan shows good bone marrow imaging without evidence of metastatic defects. She is now a candidate for **treatment** of other sites of her metastatic breast **cancer**.

US PAT NO: 5,776,093 [IMAGE AVAILABLE] L11: 5 of 105
DETDESC:

DETD(5)

A middle-age woman with advanced breast **cancer**, including bone and bone marrow invasion, has an aliquot of her bone marrow removed and harvested for regrafting after clearing the marrow of the **cancer** cells in vitro. The bone marrow in the patient is then destroyed by i.v. infusion of 20 mg NP-2 monoclonal antibody F(ab').sub.2 labeled with 200 mCi Rhenium-188 according to the method of Griffiths et al. (**Cancer** Res. 51:4594, 1991). Approximately 3 weeks later, there is evidence of severe bone marrow toxicity which requires the infusion of the autologous bone marrow which was previously cleared of **cancer** cells, in combination with hematopoietic growth factor administration, in this case with **GM**-**CSF** given repeatedly before and after marrow grafting. Six weeks later, the patient has renewed bone marrow function and an MN3-Fab'. . . (Tc-99m) bone marrow scan shows good bone marrow imaging without evidence of metastatic defects. She is now a candidate for **treatment** of other sites of her metastatic breast **cancer**.

US PAT NO: 5,766,897 [IMAGE AVAILABLE] L11: 6 of 105
DETDESC:

DETD(151)

Where . . . may be found in U.S. Pat. Nos. 5,292,724 and 5,182,259; guidance for administration of human growth hormone (hGH) in the **treatment** of individuals intoxicated with poisonous substances may be found in U.S. Pat. Nos. 5,140,008 and 4,816,439; guidance for administration of hGH in the **treatment** of topical ulcers may be found in U.S. Pat. No. 5,006,509; guidance for administration of (EPO) for **treatment** of anemia and pulmonary administration of EPO may be found in U.S. Pat. No. 5,354,934; guidance for administration of EPO, **GM**-**CSF**, G-CSF, and multi-CSF for **treatment** of pancytopenia may be found in U.S. Pat. No. 5,198,417; guidance for administration of EPO for treating iron overload may be found in U.S. Pat. No. 5,013,718; guidance for administration of EPO in the **treatment** of hemoglobinopathies may be found in U.S. Pat. No. 4,965,251; guidance for administration of insulin the **treatment** of diabetes may be found in U.S. Pat. No. 4,478,822; guidance for delivery of asparaginase for **treatment** of neoplasms may be found in U.S. Pat. Nos. 4,478,822 and 4,474,752; guidance for administration of L-asparaginase in the **treatment** of tumors is found in U.S. Pat. No. 5,290,773; guidance for administration of prostaglandin E1, prostaglandin E2, prostaglandin F2 alpha,. . . chymopapain, bromelain, chymotrypsin, streptokinase, urokinase, tissue plasminogen activator, fibrinolysin, deoxyribonuclease, sutilains, collagenase, asparaginase, or heparin in a cryogel bandage for **treatment** of sites of trauma may be found in U.S. Pat. No. 5,260,066; guidance for the administration of superoxide dismutase, glucocerebrosides,. . . deaminase, interferons (alpha, beta, and gamma), interleukin (1,2,3,4,5,6,7), tissue necrosis factor (TNF-alpha or TNF-beta), and colony stimulating factors (CSF, G-CSF, **GM**-**CSF**) in liposomes may be found in U.S. Pat. No. 5,225,212; guidance for administration of asparaginase or insulin in the **treatment** of neoplastic lesions may be found in U.S. Pat. No. 4,978,332; guidance for administration of asparaginase in the reduction of **tumor** growth may be found in U.S. Pat. No. 4,863,910; guidance for the administration of antibodies in the prevention of transplant. . . cells, augmentation of natural killer cell activity, induction of interferon-gamma, restoration or enhancement of cellular immunity, and augmentation of cell-mediated anti-**tumor** activity may be found in U.S. Pat. No. 5,206,344; guidance for the administration of interleukin-2 in the **treatment** of tumors may be found in U.S. Pat. No. 4,690,915; and guidance for administration of interleukin-3 in the stimulation of hematopoiesis, as a **cancer** chemotherapy, and in the **treatment** of immune disorders may be found in U.S. Pat. No. 5,166,322.

US PAT NO: 5,763,415 [IMAGE AVAILABLE] L11: 7 of 105
DETDESC:

DETD(16)

The present invention also provides a method of treating the ductal epithelium of a mammary gland both therapeutically and prophylactically for **cancer**. The method comprises treating the mammary gland therapeutically with any given therapeutic method, such as those currently known and used. . . the cancerous tissue, radiation therapy and chemotherapy. The method further comprises contacting, either concomitantly with or subsequently to the therapeutic **treatment**, the ductal epithelium of the mammary gland, e.g., by ductal cannulation, with an epithelium-destroying agent, which preferably does not specifically target cancerous cells, so as to destroy any remaining cancerous cells and noncancerous cells and inhibit the spread of **cancer**. The epithelium-destroying agent is preferably a vector comprising a thymidine kinase gene, such as a Herpes simplex thymidine kinase gene,. . . or ethanol. The method can additionally comprise contacting the ductal epithelium with a cytokine or hematopoietic growth factor, such as **GM**-**CSF**.

US PAT NO: 5,750,529 [IMAGE AVAILABLE] L11: 8 of 105
SUMMARY:

BSUM(11)

Recently, **cancer** **treatment** with anti-Apo-I antibody has been attempted as an apoptosis-related therapy. Among the myelodysplastic syndrome (MDS), refractory anemia (RA) and refractory. . . be treated with a combination of retinoic acid or vitamin D.sub.3, which is a differentiation inducer for hemopoietic cells, and **GM**-**CSF** or IL-3 as an apoptosis regulating agent which suppresses excessive apoptosis of platelet producing cells whereas, in RAEB (refractory anemia. . .

US PAT NO: 5,739,110 [IMAGE AVAILABLE] L11: 9 of 105
DETDESC:

DETD(6)

Interleukin-1 . . . Immunol. 140:3830, 1988; Futami, H., et al., J. Immunol. 145:4121, 1990; Fibbe, W. E., et al., Exp. Hematol. 17:805, 1989). **GM**-**CSF** and G-CSF have

also been found to have marked restorative effects after irradiation (Tanikawa, S., et al., Exp. Hematol. 17:883, 1989; Schuening, F. G., et al., Blood 74:1308, 1989) or **treatment** with chemotherapeutic drugs both in preclinical models (Moore, M. A. S., et al., Proc. Natl. Acad. Sci. USA 84:7134, 1987;. . . Welte, K., et al., J. Exp. Med. 165:941, 1987), as well as in human trials (Steward, W. P., et al., **Cancer** Treat. Rev. 17:77, 1990; Gianni, A. M., et al., J. Clin. Oncol. 8:768, 1990).

US PAT NO: 5,726,181 [IMAGE AVAILABLE] L11: 10 of 105
SUMMARY:

BSUM(117)

A further embodiment of claimed HLCD is a method of **treatment** of **cancer** in humans with convergent therapy or combination therapy. This method uses HLCD dissolved in NMP, in the presence of pharmaceutically. . . bleomycin, mitomycin-C, fluoxymesterone, mechlorethamine, teniposide, hexamethylmelamine, leucovorin, melphelan, methotrexate, mercaptopurine, mitoxantrone, BCNU, CCNU, procarbazine, vincristine, vinblastine, vindesine, thioTEPA, amsacrine, G-CSF, **GM**-**CSF**, erythropoietin, .gamma.-methylene-10-deazaaminopterin or .gamma.-methylene-10-ethyl-10-deazaaminopterin, taxol, and 5-azacytidine. For the purpose of this invention, the terms convergent, co-administered, and combination are. . .

US PAT NO: 5,725,850 [IMAGE AVAILABLE] L11: 11 of 105
SUMMARY:

BSUM(6)

GM-**CSF** is described by Gough, et al, Nature (1984) 309:763-767. This protein is further described in W087/02060, published 9 Apr. 1987 as being useful to treat **cancer** patients to regenerate leukocytes after traditional **cancer** **treatment**, and to reduce the likelihood of viral, bacterial, fungal and parasitic infection, such as acquired immune deficiency syndrome (AIDS). Human. . .

US PAT NO: 5,720,952 [IMAGE AVAILABLE] L11: 12 of 105
CLAIMS:

CLMS(4)

4. The method of claim 3, wherein said **GM**-**CSF** protein is administered to a mammal with **cancer** following chemotherapeutic or irradiation **treatment** of said **cancer**.

US PAT NO: 5,716,981 [IMAGE AVAILABLE] L11: 13 of 105
SUMMARY:

BSUM(7)

Lymphokines have also been utilized in the **treatment** of **cancer**. Briefly, lymphokines are secreted by a variety of cells, and generally have an effect on specific cells in the generation. . . response. Examples of lymphokines include Interleukins (IL)-1, -2, -3, and -4, as well as colony stimulating factors such as G-CSF, **GM**-**CSF**, and M-CSF. Recently, one group has utilized IL-2 to stimulate peripheral blood cells in order to expand and produce large quantities of cells which are cytotoxic to **tumor** cells (Rosenberg et al., N. Engl. J. Med. 313:1485-1492, 1985).

US PAT NO: 5,705,151 [IMAGE AVAILABLE] L11: 14 of 105
DETDESC:

DETD(110)

This example describes the **treatment** of canine **melanoma** with DNA encoding superantigen or **GM**-**CSF**.

DETDESC:

DETD(116)

TABLE 1

Patient Log for SEB.S and PCR.sub.3 -GM DNA **Treatment** of Canine **Melanoma**

Patient	Stage	TN	**Tumor** Size	Start Date	Response	Comments
Zomax	I	T1bNOMO	1.5 cm diam	5/16/94	CR 51 wks	SEB.S + **GM**-**CSF**
Shadow	III	T2bN1bMO	3 cm diam	5/23/94	CR 50 wks	SEB.S + **GM**-**CSF**
NG	I	T1NOMO	1.2 cm diam	9/12/94	CR 34 wks	SEB.S + **GM**-**CSF**
Maggie	II	T2aNOMO	2 cm diam	8/24/94	PR 33 wks	SEB.S + **GM**-**CSF**
K. C.	III	T3aNOMO	>4 cm diam			

10/13/94
SD 12 wk
SEB.S + **GM**-**CSF**

Belvedere
III
T2N1bMO
4 cm diam
10/13/94
CR 30 wks
SEB.S + **GM**-**CSF**

Nicholas
III
T3bNOMO
>4 cm diam
2/15/95
SD 12 wks
SEB.S + **GM**-**CSF**

Heidi
III
TON1bMO
LN: 2 cm diam
2/27/95
PR 10 wks
SEB.S + **GM**-**CSF**

Bear III
TON1bMO
LN: 2.5 cm
4/11/95
SD 4 wks
SEB.S + **GM**-**CSF**

Key to terminology in patient data sheets:
Stage: I represents the smallest and III the largest size, with metastase
TNM: World Health Organization staging system
SD = stable disease (no **tumor** growth)
PR = partial remission (>50% decrease in **tumor** size)
CR = **tumor** completely regressed
PD = progressive disease, no response to **treatment**
MCT = mast cell **tumor**
Mammary CA = mammary gland adenocarcinoma (malignant breast **cancer**) Thyroid CA = thyroid adenocarcinoma
SCC = squamous cell carcinoma

DETDESC:

DETD(117)

The results shown in Table 1 indicate that a **treatment** response was observed in 6 of 9 dogs treated for the 12 week trial period. This included 4 complete remissions (no residual **tumor**) and 2 partial remissions (greater than 50% reduction in **tumor** size). Tumors in the remaining two dogs did not regress, but also did not progress in size during the 12 week trial. On average, a **tumor** response required 6 to 10 weeks to become apparent. The injections did not cause any inflammation or necrosis at injections. . . this study. These results provide evidence of the efficacy of direct DNA injection using DNA encoding superantigen (SEB) and cytokine (**GM**-**CSF**) for **treatment** of spontaneous malignant **melanoma** in an outbred species.

DETDESC:

DETD(122)

TABLE 2

Patient Log for SEB.S or PCR.sub.3 -GM DNA alone **Treatment** of Canine **Melanoma**
Patient
Stage
TN **Tumor** Size
Start Date
Response
Comments

Jessie
II T2bNOMO
2 cm diam
1/11/95
PD. . . 12 wks
SEB.S alone

Scooter
I T2aNOMO
2 cm diam
3/24/95
PD 7 wks
GM-**CSF** alone

DETDESC:

DETD(125)

This example describes the **treatment** of various **tumor** types with superantigen or **GM**-**CSF** encoding DNA.

DETDESC:

DETD(128)

TABLE 3

Patient Log for SEB.S and PCR.sub.3 -GM DNA **Treatment** of Various Carcinomas
Patient
Tumor Type
Stage
TN **Tumor** Size
Start Date
Response
Comments

Emma
Mammary CA
III
T4N1bNMO
1.8 cm diam
8/11/94

PR 22 wks
SEB.S + **GM**-**CSF** Baby
Mammary CA
II T1aN1bMO
2.6 cm diam
9/12/94
PR 8 wks
SEB.S + **GM**-**CSF** Christa
MCT IIIa
NA >2 cm diam
7/27/94
SD 39 wks
SEB.S + **GM**-**CSF** Jack
MCT IIIa
NA >3 cm diam
3/28/95
PD 4 wks
SEB.S + **GM**-**CSF** Britt
Thyroid CA
III
T3bNOMO
>7 cm diam
10/14/94
SD 16 wk
SEB.S + **GM**-**CSF** Duncan
Melanoma Toe
NA*
T2N1MO
>4 cm diam
8/11/94
SD 20 wks
SEB.S + **GM**-**CSF** Billy
Melanoma Toe
NA*
TON1bMO
LN 3.5 cm
1/10/95
CR 17 wks
SEB.S + **GM**-**CSF** Scotche
SCC Tonsil
NA T3NOMO
4 cm diam
3/27/95
SD SEB.S + **GM**-**CSF**

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*Metastases
NA Not Applicable
CA Carcinoma
MCT Mast Cell **Tumor**
SCC Squamous Cell Carcinoma

US PAT NO: 5,702,919 [IMAGE AVAILABLE] L11: 15 of 105
DETDESC:

DETD(34)

The in vivo effect of **GM**-**CSF** on megakaryocytes and platelets is not well delineated. Platelet counts varied in different animal studies with no changes observed in. . . treated with hGM-CSF [25,51,53] (Farese, A.). Thrombocytopenia has been reported as a complication in several clinical studies of patients with **cancer** or acquired immunodeficiency syndrome receiving hGM-CSF [52-54]. The possibility of exacerbation of an otherwise stable or subclinical autoimmune thrombocytopenia was. . . also been reported in patients with aplastic anemia that platelet counts 1 hour after platelet transfusion were lower, while on **treatment** with hGM-CSF, were comparable to pre-**treatment** increments [55]. Other studies have shown no significant change, or, in some patients with myelodysplasia, an increase in platelet counts. . .

US PAT NO: 5,697,902 [IMAGE AVAILABLE] L11: 16 of 105
DETDESC:

DETD(5)

A middle-age woman with advanced breast **cancer**, including bone and bone marrow invasion, has an aliquot of her bone marrow removed and harvested for regrafting after clearing the marrow of the **cancer** cells in vitro. The bone marrow in the patient is then destroyed by i.v. infusion of 20 mg NP-2 monoclonal antibody F(ab').sub.2 labeled with 200 mCi Rhenium-188 according to the method of Griffiths et al. (**Cancer** Res. 51:4594, 1991). Approximately 3 weeks later, there is evidence of severe bone marrow toxicity which requires the infusion of the autologous bone marrow which was previously cleared of **cancer** cells, in combination with hematopoietic growth factor administration, in this case with **GM**-**CSF** given repeatedly before and after marrow grafting. Six weeks later, the patient has renewed bone marrow function and an MN3-Fab'. . . (Tc-99m) bone marrow scan shows good bone marrow imaging without evidence of metastatic defects. She is now a candidate for **treatment** of other sites of her metastatic breast **cancer**.

US PAT NO: 5,693,522 [IMAGE AVAILABLE] L11: 17 of 105
SUMMARY:

BSUM(7)

Lymphokines have also been utilized in the **treatment** of **cancer**. Briefly, lymphokines are secreted by a variety of cells, and generally have an effect on specific cells in the generation. . . response. Examples of lymphokines include Interleukins (IL)-1, -2, -3, and -4, as well as colony stimulating factors such as G-CSF, **GM**-**CSF**, and M-CSF. Recently, one group has utilized IL-2 to stimulate peripheral blood cells in order to expand and produce large quantities of cells which are cytotoxic to **tumor** cells (Rosenberg et al., N. Engl. J. Med. 323:1485-1492, 1985).

US PAT NO: 5,691,341 [IMAGE AVAILABLE] L11: 18 of 105
SUMMARY:

BSUM(18)

Recently, **cancer** **treatment** with anti-Apo-I anti-body has been attempted as an apoptosis-related therapy. Among the myelodysplastic syndrome (MDS), refractory anemia (RA) and refractory. . . treated with a combination of retinoic acid or active-type vitamin D.sub.3, which is a differentiation inducer for hemopoietic cells, and **GM**-**CSF** or IL-3 as an

apoptosis regulating agent which suppresses excessive apoptosis of platelet producing cells whereas, in RAEB (refractory anemia. . .

US PAT NO: 5,681,719 [IMAGE AVAILABLE] L11: 19 of 105
SUMMARY:

BSUM(13)

Human and murine **GM**-**CSF**, which is a CSF protein of a different subclass, has been purified and the cDNAs cloned. This protein was shown to be distinct from other CSFs, e.g., CSF-1 (18). This **GM**-**CSF** protein is further described in PCT No. WO87/02060, published Apr. 9, 1987, as being useful to treat **cancer** patients to regenerate leukocytes after traditional **cancer** **treatment**, and to reduce the likelihood of viral, bacterial, fungal, and parasitic infection, such as in acquired immune deficiency syndrome (AIDS).

US PAT NO: 5,674,874 [IMAGE AVAILABLE] L11: 20 of 105
SUMMARY:

BSUM(147)

A further aspect of this invention is that HECPT is a method of **treatment** of **cancer** in humans with convergent therapy or combination drug therapy. This method uses 7-ethyl-10-hydroxy camptothecin dissolved in dimethylisosorbide (DMI) or dimethylacetamide. . . bleomycin, mitomycin-C, fluoxymesterone, mechlorethamine, teniposide, hexamethylmelamine, leucovorin, melphelan, methotrexate, mercaptopurine, mitoxantrone, BCNU, CCNU, procarbazine, vincristine, vinblastine, vindesine, thioTEPA, amsacrine, G-CSF, **GM**-**CSF**, erythropoietin,.sub.-- .gamma.-methylene-10-deazaaminopterin or.sub.-- .gamma.-methylene-10-ethyl-10-deazaaminopterin, taxol, and 5-azacytidine. For the purpose of this invention, the terms convergent, co-administered, and combination are. . .

US PAT NO: 5,674,873 [IMAGE AVAILABLE] L11: 21 of 105
SUMMARY:

BSUM(108)

A further embodiment of claimed HECPT is a method of **treatment** of **cancer** in humans with convergent therapy or combination therapy. This method uses 10-hydroxy 7-ethyl camptothecin dissolved in dimethylisosorbide (DMI) or dimethylacetamide. . . bleomycin, mitomycin-C, fluoxymesterone, mechlorethamine, teniposide, hexamethylmelamine, leucovorin, melphelan, methotrexate, mercaptopurine, mitoxantrone, BCNU, CCNU, procarbazine, vincristine, vinblastine, vindesine, thioTEPA, amsacrine, G-CSF, **GM**-**CSF**, erythropoietin, .gamma.-methylene-10-deazaaminopterin or ,.gamma.-methylene-10-ethyl-10- deazaaminopterin, taxol, and 5-azacytidine. For the purpose of this invention, the terms convergent, co-administered, and combination are. . .

US PAT NO: 5,674,694 [IMAGE AVAILABLE] L11: 22 of 105
CLAIMS:

CLMS(16)

16. A method for determining the effectiveness of a bone marrow **treatment** technique comprising, testing a specimen of bone marrow cells prior to a **treatment** (pre-**treatment** cells) and a specimen of bone marrow cells after a **treatment** (post-**treatment** cells) for **tumor** cells of interest by:
(a) plating each specimen on homogeneous culture media which supports growth of bone marrow cells comprising. . . factor which stimulates the growth of cells of interest wherein the growth factor is selected from the group consisting of **GM**-**CSF** at a concentration of about 20 to about 150 U/ml of media, EGF at a concentration of about 1 to. . . number of individual clones of cells of interest, resulting from the culturing of each specimen; wherein,
(d) no clonogenic growth of post-**treatment** **tumor** cells indicates effectiveness of the bone marrow **treatment** technique.

US PAT NO: 5,672,603 [IMAGE AVAILABLE] L11: 23 of 105
SUMMARY:

BSUM(11)

Recently, **cancer** **treatment** with anti-Apo-I antibody has been attempted as an apoptosis-related therapy. Among the myelodysplastic syndrome (MDS), refractory anemia (RA) and refractory. . . be treated with a combination of retinoic acid or vitamin D3, which is a differentiation inducer for hemopoietic cells, and **GM**-**CSF** or IL-3 as an apoptosis regulating agent which suppresses excessive apoptosis of platelet producing cells whereas, in RAEB (refractory anemia. . .

US PAT NO: 5,672,493 [IMAGE AVAILABLE] L11: 24 of 105
SUMMARY:

BSUM(5)

Development . . . been applied to treatments using immunologic reagents and other substances derived from biologic sources to distinguish these from conventional surgical **treatment**, radiation therapy, and chemotherapy. Thus, immunologic approaches for the **treatment** of **cancer**, HIV/ARC, and immune compromised patients, including infection/inflammatory conditions, are being actively pursued. For example, the development of cloned recombinant human gene products, including granulocyte-macrophage colony stimulating factor (**GM**-**CSF**), three species of interferon (IFN), interleukin-2 (IL-2), and **tumor** necrosis factor-.alpha. (TNF-.alpha.) has led to their testing in clinical trials, albeit with varying degrees of success (Lotze, M. T.. . . on hematologic malignancies, including CML, hairy cell leukemia, non-Hodgkin's lymphoma, and cutaneous T-cell lymphoma, as well as administration of IL-2, **GM**-**CSF**, lymphokines-activated <------User Break------> parasitic infection, such as in acquired immune deficiency syndrome (AIDS).

US PAT NO: 5,670,351 [IMAGE AVAILABLE] L11: 27 of 105
SUMMARY:

BSUM(18)

The . . . liters of peripheral blood would collect approximately 10.sup.5 CFU-GM although this number could be increased to 10.sup.6 CFU-GM by prior **treatment** of the donor with **GM**-**CSF**. Rapid recovery of a patient would require transfusion of approximately 1.times.10.sup.8 to 5.times.10.sup.8 CFU-GM which is 100 to 1,000 times. . . peripheral blood to increase the number of CFU-GM 2 to 3 orders of magnitude would significantly affect chemotherapy administration and **Cancer** **treatment**.

US PAT NO: 5,670,147 [IMAGE AVAILABLE] L11: 28 of 105
SUMMARY:

BSUM(18)

The . . . liters of peripheral blood would collect approximately 10.sup.5 CFU-GM although this number could be increased to 10.sup.6 CFU-GM by prior **treatment** of the donor with **GM**-**CSF**. Rapid recovery of a patient would require transfusion of approximately 1.times.10.sup.8 to 5.times.10.sup.8 CFU-GM which is 100 to 1,000 times. . . peripheral blood to increase the number of CFU-GM 2 to 3 orders of magnitude would significantly affect chemotherapy administration and **cancer** **treatment**.

US PAT NO: 5,662,896 [IMAGE AVAILABLE] L11: 29 of 105
SUMMARY:

BSUM(7)

Lymphokines have also been utilized in the **treatment** of **cancer**. Briefly, lymphokines are secreted by a variety of cells, and generally have an effect on specific cells in the generation. . . response. Examples of lymphokines include Interleukins (IL)-1, -2, -3, and -4, as well as colony stimulating factors such as G-CSF, **GM**-**CSF**, and M-CSF. Recently, one group has utilized IL-2 to stimulate peripheral blood cells in order to expand and produce large quantities of cells which are cytotoxic to **tumor** cells (Rosenberg et al., N. Engl. J. Med. 313:1485-1492, 1985).

US PAT NO: 5,658,912 [IMAGE AVAILABLE] L11: 30 of 105
SUMMARY:

BSUM(11)

Recently, **cancer** **treatment** with anti-Apo-I antibody has been attempted as an apoptosis-related therapy. Among the myelodysplastic syndrome (MDS), refractory anemia (RA) and refractory. . . be treated with a combination of retinoic acid or vitamin D.sub.3, which is a differentiation inducer for hemopoietic cells, and **GM**-**CSF** or IL-3 as an apoptosis regulating agent which suppresses excessive apoptosis of platelet producing cells whereas, in RAEB (refractory anemia. .

US PAT NO: 5,652,225 [IMAGE AVAILABLE] L11: 31 of 105
DETDESC:

DETD(3)

The . . . cells provides a therapeutic effect. The nucleic acid is selected based upon the desired therapeutic outcome. For example, in the **treatment** of ischemic diseases, one genetic material of choice would be a DNA encoding an angiogenic protein. DNA useful in the. . . DNA's of interest include those encoding hemoglobin, interleukin-1, interleukin-2, interleukin-3, interleukin-4, interleukin-4, interleukin-5, interleukin-6, interleukin-7, interleukin-8, interleukin-9, interleukin-10, interleukin-11, etc., **GM**-**CSF**, G-CSF, M-CSR, human growth factor, insulin, factor VIII, factor IX, tPA, LDL receptors, **tumor** necrosis factor, PDGF, EGF, NGF, IL-1ra, EPO, .beta.-globin and the like, as well as biologically active muteins of these proteins.. . .

US PAT NO: 5,652,095 [IMAGE AVAILABLE] L11: 32 of 105
SUMMARY:

BSUM(9)

An . . . de novo AML and de novo acute lymphocytic leukemia (ALL), respectively (Van den Berghe et al., Nature 251: 437 (1974), **Cancer** Genet. Cytogenet. 17: 189-255 (1985); Fourth International Workshop on Chromosomes in Leukemia, (1982); Le Beau et al., J. Clin. Oncol.. . . (1978); Golomb et at., Blood 60: 404-411 (1982)) or with previous exposure to alkylating agent chemotherapy or radiotherapy for the **treatment** of various malignancies (Le Beau et al., ibid. (1986)). A series of studies have revealed that the smallest commonly deleted. . . genes have been mapped to the 5q31 region, including the hematopoietic growth factors and interleukins IL-3, IL-4, IL-5, IL-9, and **GM**-**CSF**, and, the EGR-1 transcription factor (Huebner et at., Science 230: 1282-1285 (1985); Le Beau et al., Science 231: 984-987 (1986). . . at., Genomics 13: 803-808 (1992)). However, none of these genes currently appear to fulfill the requirements expected of a candidate **tumor** suppressor gene. Loss of one IL-3, IL-4, IL-5, and **GM**-**CSF** allele has been frequently, though not consistently, reported in leukemia and MDS patients with del(5q) (Le Beau et at., ibid.. . . EGR-1 in del(5q) patients have yielded similar negative findings (G. Gilliland et at., Harvard University, personal communication). Thus, a candidate **tumor** suppressor gene remained to be identified in this region.

US PAT NO: 5,649,904 [IMAGE AVAILABLE] L11: 33 of 105
SUMMARY:

BSUM(5)

It is known that **GM**-**CSF** is a factor which is required for the survival, proliferation and differentiation of myeloid progenitor cells which are committed to. . . and macrophages (CFU-GMs). G-CSF similarly acts on myeloid progenitor cells committed to form mature granulocytes. Each is useful in the

treatment of myelo-suppression caused by chemotherapeutic or irradiation **treatment** of **cancer**. Under such circumstances the HPSF is administered to a patient, treated with chemo- or irradiation therapy, after the re-infusion of. . . bone marrow) in order to stimulate the proliferation and differentiation of the myeloid progenitor cells found in the bone marrow. **GM**-**CSF** may also be administered for 3-5 days before the removal of bone marrow for later re-infusion.

DETDESC: u
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7. DIALOG Business Connection(R) and DIALOG Headlines(SM) 8. DIALOG(R) Document Delivery
9. Data Star(R)
10. Other Online Menu Services & Files (MoneyCenter(R), BNA, etc.)
(c) 1998 The Dialog Corporation plc All rights reserved.
/H = Help /L = Logoff /NOMENU = Command Mode
Enter an option number to view information or to connect to an online service. Enter a BEGIN command plus a file number to search a database (e.g., B1 for ERIC).
? b 410

06aug98 16:11:22 User217743 Session D451.1
$0.00 0.149 DialUnits FileHomeBase
$0.00 Estimated cost FileHomeBase
$0.00 Estimated cost this search
$0.00 Estimated total session cost 0.149 DialUnits
File 410:Chronolog(R) 1981-1998/Jul/Aug
(c) 1998 The Dialog Corporation plc

Set Items Description
--- ----- -----------
? set hi %%%;set hi %%%

HILIGHT set on as '%%%'%%%
%%%HILIGHT set on as '%%%'
? b 411

06aug98 16:11:34 User217743 Session D451.2
$0.00 0.107 DialUnits File410
$0.00 Estimated cost File410
$0.00 Estimated cost this search
$0.00 Estimated total session cost 0.257 DialUnits File 411:DIALINDEX(R)

DIALINDEX(R)
(c) 1998 The Dialog Corporation plc

*** DIALINDEX search results display in an abbreviated *** *** format unless you enter the SET DETAIL ON command. *** ? set files biochem

>>> 162 is unauthorized
>>> 352 is unauthorized
>>>2 of the specified files are not available
You have 33 files in your file list.
(To see banners, use SHOW FILES command)
? s (mage()3) and (gmcsf or gm()csf)

Your SELECT statement is:
s (mage()3) and (gmcsf or gm()csf)

```
      Items   File
      -----   ----
        4     5: BIOSIS PREVIEWS(R)_1969-1998/JUL W4
        6     34: SciSearch(R) Cited Ref Sci_1990-1998/Jul W4
        2     71: ELSEVIER BIOBASE_1994-1998/Aug W1
        3     73: EMBASE_1974-1998/Aug W2
        1     76: Life Sciences Collection_1982-1998/Jun
    2   94: JICST-EPlus_1985-1998/May W4
        1     144: Pascal_1973-1998/Jul
        2     155: MEDLINE(R)_1966-1998/Sep W4
        1     351: DERWENT
WPI_1963-1998/UD=9830;UP=9827;UM=9825          1
377: Derwent Drug File_1983-1998/Jul W4        1   399:
CA SEARCH(R)_1967-1998/UD=12905

  11 files have one or more items; file list includes 33 files.
? rf

Your last SELECT statement was:
  S (MAGE()3) AND (GMCSF OR GM()CSF)

Ref      Items   File
---      -----   ----
N1           6   34: SciSearch(R) Cited Ref Sci_1990-1998/Jul
W4 N2        4   5: BIOSIS
PREVIEWS(R)_1969-1998/JUL W4 N3          3   73:
EMBASE_1974-1998/Aug W2
N4           2   71: ELSEVIER BIOBASE_1994-1998/Aug W1
N5           2   94: JICST-EPlus_1985-1998/May W4
N6           2   155: MEDLINE(R)_1966-1998/Sep W4
N7           1   76: Life Sciences Collection_1982-1998/Jun N8
         1   144: Pascal_1973-1998/Jul
N9           1   351: DERWENT
WPI_1963-1998/UD=9830;UP=9827;UM=9825 N10        1
377: Derwent Drug File_1983-1998/Jul W4   11 files have one
or more items; file list includes 33 files.
      - Enter P or PAGE for more -
? b 155

    06aug98 16:13:29 User217743 Session D451.3
       $2.00   2.000 DialUnits File411
   $2.00  Estimated cost File411
   $2.00  Estimated cost this search
   $2.00  Estimated total session cost   2.257 DialUnits
File 155:MEDLINE(R)  1966-1998/Sep W4
    (c) format only 1998 Dialog Corporation

    Set  Items  Description
    ---  -----  -----------
? s (mage()3) and (gmcsf or gm()csf)

        248  MAGE
      1563270  3
         86  MAGE(W)3
         85  GMCSF
      19677  GM
      31490  CSF
       6565  GM(W)CSF
    S1     2  (MAGE()3) AND (GMCSF OR GM()CSF)
? t s1/3,ab/1,2


 1/3,AB/1
DIALOG(R)File 155:MEDLINE(R)
(c) format only 1998 Dialog Corporation. All rts. reserv.

09292446  97477808
 Transfection of IL-2 augments CTL response to human
melanoma cells in vitro: immunological characterization of a
melanoma vaccine.  van Elsas A; Aarnoudse C; van der Minne
CE; van der Spek CW; Brouwenstijn N; Osanto S; Schrier PI
 Department of Clinical Oncology, University Hospital
Leiden, The Netherlands.
 J Immunother (UNITED STATES)  Sep 1997,  20 (5)
p343-53, ISSN 1053-8550 Journal Code: CUQ
 Languages: ENGLISH
 Document type: JOURNAL ARTICLE
 We have transfected human melanoma cell line 518A2 with
the cDNA encoding interleukin-2 (IL-2) or
granulocyte-macrophage colony-stimulating factor (
%%%GM%%%-%%%CSF%%% ), and compared
cytokine-producing clones for their ability to induce
melanoma-specific cytotoxic T lymphocytes (CTL) from
autologous peripheral blood mononuclear cells (PBMC) in vitro.
The parental cell line expressed HLA-A1, HLA-A2, ICAM-1,
LFA-3, in addition to the common CTL antigens MAGE-1,
%%%MAGE%%%-%%%3%%% , tyrosinase, gp100, and
Melan-A/MART-1.  Stimulation of autologous PBMC
responders with the IL-2-transfected clone 518/IL2.14
specifically induced CTL lines reactive with all cell lines
derived from the autologous patient. Strikingly,
%%%GM%%%-%%%CSF%%% -transfected 518A2 cells
did not induce anti-tumor CTL reactivity.  CTL induction
against 518/IL2.14 was independent of HLA class II
expression or CD4 help. The parental cell line 518A2 gained
immunogenic properties when high concentrations of IL-2
were supplied exogenously, indicating that IL-2 produced and
present at high levels locally by itself enhanced
immunogenicity. From the autologous CTL line reactive
with 518/IL2.14, clones were generated against an as yet
unknown antigen, which was present in all autologous
melanoma cell lines as well as in 7 of 15 HLA-A2+ melanoma
cell lines tested, but not in melanocytes. These results will be
discussed with respect to the possibility of using
IL-2-transfected melanoma cells as a vaccine for treatment of
patients with melanoma.

 1/3,AB/2
DIALOG(R)File 155:MEDLINE(R)
(c) format only 1998 Dialog Corporation. All rts. reserv.

08881361  97053992
 Induction of antigen-specific tumor immunity by genetic
and cellular vaccines against MAGE: enhanced tumor
protection by coexpression of granulocyte-macrophage
colony-stimulating factor and B7-1.  Bueler H; Mulligan RC
 Howard Hughes Medical Institute, Children's Hospital,
Boston, Massachusetts, USA.
 Mol Med (UNITED STATES)  Sep 1996,  2 (5) p545-55,
ISSN 1076-1551 Journal Code: CG3
 Contract/Grant No.: CA63399, CA, NCI
 Languages: ENGLISH
 Document type: JOURNAL ARTICLE
 BACKGROUND: A number of tumors express antigens that
are recognized by specific cytotoxic T cells. The normal host
immune responses, however, are not usually sufficient to
cause tumor rejection. Using appropriate immunization
strategies, tumor-specific antigens may serve as targets
against which tumor-destructive immune responses can be
generated. MAGE-1 and %%%MAGE%%%-%%%3%%%
are two clinically relevant antigens expressed in many human
melanomas and other tumors, but not in normal tissues,
except testis. Here, we have investigated whether DNA
and cellular vaccines against MAGE-1 and
%%%MAGE%%%-%%%3%%% can induce
antigen-specific anti-tumor immunity and cause rejection of
MAGE-expressing tumors. MATERIALS AND METHODS:
Mice were immunized against MAGE-1 and
```

late, but get -

%%%MAGE%%%- %%%3%%% by subcutaneous injection of genetically modified embryonic fibroblasts or intramuscular injection of purified DNA. Mice were injected with lethal doses of B16 melanoma cells expressing the corresponding MAGE antigens or the unrelated protein SIV tat, and tumor development and survival were monitored. RESULTS: Intramuscular expression of MAGE-1 and %%%MAGE%%%-%%%3%%% by plasmid DNA injection and subcutaneous immunization with syngeneic mouse embryonic fibroblasts transduced with recombinant retroviruses to express these antigens induced specific immunity against tumors expressing MAGE-1 and %%%MAGE%%%-%%%3%%%. Both CD4+ and CD8+ T cells were required for anti-tumor immunity. Coexpression of granulocyte-macrophage colony-stimulating factor (%%%GM%%%-%%%CSF%%%) or B7-1 significantly increased anti-tumor immunity in an antigen-specific manner and resulted in a considerable proportion of mice surviving lethal tumor challenge. CONCLUSIONS: Our results suggest that genetic and cellular vaccines against MAGE and other tumor antigens may be useful for the therapy of tumors expressing specific markers, and that %%%GM%%%-%%%CSF%%% and B7-1 are potent stimulators for the induction of antigen-specific tumor immunity.

? s (gmcsf or gm()csf)

```
        85 GMCSF
     19677 GM
     31490 CSF
      6565 GM(W)CSF
S2   6643 (GMCSF OR GM()CSF)
```

? s s2 and fusion()protein

```
      6643 S2
     63265 FUSION
    744852 PROTEIN
      7988 FUSION(W)PROTEIN
S3     86 S2 AND FUSION()PROTEIN
```

? s (gmcsf or gm()csf)(p)(anchor or membrane()attach? or transmembrane)
>>>Invalid syntax
? s (gmcsf or gm()csf)(5np)(anchor or membrane()attach? or transmembrane)
>>>Invalid syntax
? s (gmcsf or gm()csf)(5n)(anchor or membrane()attach? or transmembrane)

```
        85 GMCSF
     19677 GM
     31490 CSF
      6565 GM(W)CSF
      3886 ANCHOR
    405145 MEMBRANE
     59019 ATTACH?
       478 MEMBRANE(W)ATTACH?
     22672 TRANSMEMBRANE
S4     4 (GMCSF OR GM()CSF)(5N)(ANCHOR OR MEMBRANE()ATTACH? OR TRANSMEMBRANE)
```

? t s4/3,ab/all

4/3,AB/1
DIALOG(R)File 155:MEDLINE(R)
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09047532 97266587
Oligomerization of the soluble granulocyte-macrophage colony-stimulating factor receptor: identification of the functional ligand-binding species. Brown CB; Pihl CE; Murray EW
Department of Medicine, The University of Calgary, Alberta, Canada. cbrown@acs.ucalgary.ca
Cytokine (UNITED STATES) Apr 1997, 9 (4) p219-25, ISSN 1043-4666 Journal Code: A52
Languages: ENGLISH
Document type: JOURNAL ARTICLE
The ligand-specific alpha subunit of the dimeric human %%%GM%%%-%%%CSF%%% receptor exists in both %%%transmembrane%%% anchored (tmGM-CSFR alpha) and soluble (sGM-CSFR alpha) isoforms. sGM-CSFR alpha binds to GM-CSF in solution and antagonizes GM-CSF biological activity in vitro. In an effort to better understand the biological properties of sGM-CSFR alpha the authors have attempted to define the exact stoichiometry of the interaction between GM-CSF and sGM-CSFR alpha. Size separation of sGM-CSFR alpha by polyacrylamide gel electrophoresis (PAGE) under non-reducing conditions demonstrated that sGM-CSFR alpha can exist in solution not only in a monomeric state but also in higher order oligomers. FPLC analysis of ligand/sGM-CSFR alpha complexes suggested that only one of these sGM-CSFR alpha species could functionally bind GM-CSF. PAGE analysis of FPLC fractions demonstrated that the peak of GM-CSF binding activity corresponded to the presence of a monomeric form of sGM-CSFR alpha. The experiments demonstrate that while sGM-CSFR alpha can adopt oligomeric forms in solution, the binding of GM-CSF to sGM-CSFR alpha most likely occurs in a (GM-CSF)1 (sGM-CSFR alpha)1 configuration.

4/3,AB/2
DIALOG(R)File 155:MEDLINE(R)
(c) format only 1998 Dialog Corporation. All rts. reserv.

08622251 96279041
Ligand-independent cell surface expression of the human soluble granulocyte-macrophage colony-stimulating factor receptor alpha subunit depends on co-expression of the membrane-associated receptor beta subunit. Murray EW; Pihl C; Morcos A; Brown CB
Department of Medicine, Cancer Biology Research Group, The University of Calgary, Calgary, Alberta, T2N 4N1 Canada.
J Biol Chem (UNITED STATES) Jun 28 1996, 271 (26) p15330-5, ISSN 0021-9258 Journal Code: HIV
Languages: ENGLISH
Document type: JOURNAL ARTICLE
The hematopoietic cytokine granulocyte-macrophage colony-stimulating factor (GM-CSF) mediates its activity through binding to cell surface receptors. The receptor for GM-CSF belongs to a superfamily of cytokine receptors characterized by a conserved extracellular motif. The high affinity %%%GM%%%-%%%CSF%%% receptor (GMR) consists of two %%%transmembrane%%% anchored subunits; a ligand binding alpha subunit (transmembrane GMRalpha) and a signal transducing beta subunit (GMRbeta), both of which belong to the cytokine receptor superfamily. The human GM-CSF receptor alpha subunit also exists in a soluble form (solGMRalpha), which antagonizes GM-CSF activity in vitro. We directly tested the potential for solGMRalpha to interact with GMRbeta in vitro. Our experiments demonstrated that exogenous solGMRalpha, even in the presence of GM-CSF, does not interact with GMRbeta on the cell surface. However, when solGMRalpha and GMRbeta are co-expressed in baby hamster kidney cells, solGMRalpha is retained on the cell surface and forms a functional intermediate affinity GM-CSF binding complex

(Kd = 331 pM). In addition, the cell surface expression of solGMRalpha is independent of the presence of GM-CSF as demonstrated using flow cytometry. Cells expressing only solGMRalpha do not show cell surface retention or form functional GM-CSF cell surface binding complexes. Sequencing of our GMRbeta clone revealed a nucleotide substitution (A --> C) resulting in the substitution of Ala for Glu at position 9 from the amino terminus of the mature GMRbeta peptide. Because the GMRbeta (A --> C) clone is capable of forming functional high affinity receptors with transmembrane GMRalpha (Kd = 64 pM), we feel that the cell surface retention of solGMRalpha is independent of the GMRbeta mutation. We suggest that the co-expression and interaction of solGMRalpha and GMRbeta represents a previously unrecognized GM-CSF receptor complex and a novel, ligand-independent mechanism of cytokine receptor assembly.

4/3,AB/3
DIALOG(R)File 155:MEDLINE(R)
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08267455 95195214
In vitro characterization of the human recombinant soluble granulocyte-macrophage colony-stimulating factor receptor. Brown CB; Beaudry P; Laing TD; Shoemaker S; Kaushansky K Department of Medicine, University of Calgary, Alberta, Canada. Blood (UNITED STATES) Mar 15 1995, 85 (6) p1488-95, ISSN 0006-4971 Journal Code: A8G
Contract/Grant No.: CA31615, CA, NCI
Languages: ENGLISH
Document type: JOURNAL ARTICLE
We have cloned, expressed, and partially purified a naturally occurring, truncated, soluble form of the human granulocyte-macrophage colony-stimulating factor (GM-CSF) receptor alpha subunit to investigate its biochemical and biologic properties. The soluble receptor species lacks the transmembrane and cytoplasmic domains that are presumably removed from the intact receptor cDNA by a mechanism of alternative splicing. The resulting soluble 55- to 60-kD glycosylated receptor species binds GM-CSF with a dissociation constant (kd) of 3.8 nmol/L. The soluble GM-CSF receptor successfully competes for %%%GM%%%-%%%CSF%%% binding not only with the %%%transmembrane%%%-anchored %%%GM%%%-%%%CSF%%% receptor alpha subunit but also with the native oligomeric high-affinity receptor complex. In addition, in human bone marrow colony-forming assays, the soluble GM-CSF receptor species can antagonize the activity of GM-CSF. Our data suggest that the soluble GM-CSF receptor may be capable of acting in vivo as a modulator of the biologic activity of GM-CSF.

4/3,AB/4
DIALOG(R)File 155:MEDLINE(R)
(c) format only 1998 Dialog Corporation. All rts. reserv.

06628070 90217679
%%%GM%%%-%%%CSF%%%: receptor structure and %%%transmembrane%%% signaling. DiPersio JF; Golde DW; Gasson JD
Department of Medicine, UCLA Medical Center 90024.
Int J Cell Cloning (UNITED STATES) Jan 1990, 8 Suppl 1 p63-74; discussion 74-5, ISSN 0737-1454 Journal Code: IJC
Languages: ENGLISH
Document type: JOURNAL ARTICLE
Human granulocyte-macrophage colony-stimulating factor (GM-CSF) both stimulates hematopoietic precursor cells to grow as well as enhances the function of mature effector cells, such as neutrophils, eosinophils and macrophages. All of the biological actions of GM-CSF appear to be mediated via binding to a single class of high-affinity receptors present on all responsive cells. Affinity cross-linking experiments demonstrate that the same 98 kDa cross-linked species seen on other GM-CSF-responsive cells is also detected on a choriocarcinoma cell line, JAR. However, JAR cells express significantly increased numbers (10,000 sites/cell) of low-affinity (Kd approximately 1.5 nM) GM receptors. The GM-CSF receptor is a glycoprotein which binds to wheat germ agglutinin-sepharose. It is dramatically downregulated on neutrophils by phorbol esters and formyl-methionyl-leucine-phenylalanine (fMLP), but not by phosphatidylinositol-dependent phospholipase C. GM-CSF primes neutrophils for enhanced response to secondary stimuli, such as ionophore and chemotactic factors. Specifically, GM-CSF enhances 3H-arachidonic acid release, synthesis of leukotriene B4 and platelet activity factor in response to fMLP and the calcium ionophores.
? ds

Set Items Description
S1 2 (MAGE()3) AND (GMCSF OR GM()CSF)
S2 6643 (GMCSF OR GM()CSF)
S3 86 S2 AND FUSION()PROTEIN
S4 4 (GMCSF OR GM()CSF)(5N)(ANCHOR OR MEMBRANE()ATTACH? OR TRAN- SMEMBRANE)
? s s3 not s4

86 S3
4 S4
S5 86 S3 NOT S4
? s s5 and anchor?

86 S5
13836 ANCHOR?
S6 0 S5 AND ANCHOR?
? t s5/6/1-10

5/6/1
09580459 98256771
A recombinant fragment of Helicobacter pylori CagA affects proliferation of human cells.

5/6/2
09528831 98254101
In vivo targeting of leukemic cells using diphtheria toxin fused to murine %%%GM%%%-%%%CSF%%%.

5/6/3
09478545 98184878
Construction and binding kinetics of a soluble granulocyte-macrophage colony-stimulating factor receptor alpha-chain-Fc %%%fusion%%% %%%protein%%%.

5/6/4
09445870 98149700
Characterization of the microheterogeneities of PIXY321, a genetically engineered granulocyte-macrophage colony-stimulating factor/interleukin-3 %%%fusion%%% %%%protein%%% expressed in yeast.

5/6/5
09427488 98119703
Interleukin-6 receptor-interleukin-6 fusion proteins with enhanced interleukin-6 type pleiotropic activities.

5/6/6
09316912 97465475
Sensitivity of human acute myeloid leukaemia to diphtheria toxin-%%%GM%%% -%%%CSF%%% %%%fusion%%% %%%protein%%%.

5/6/7
09288796 98017594
Neutrophil maturation of CD34+ cells from peripheral blood and bone marrow in serum-free culture medium with PIXY321 and granulocyte-colony stimulating factor (G-CSF).

5/6/8
09286001 98008131
Modulation of the apoptotic response of human myeloid leukemia cells to a diphtheria toxin granulocyte-macrophage colony-stimulating factor %%%fusion%%% %%%protein%%%.

5/6/9
09273184 97336614
Granulocyte-macrophage colony-stimulating factor/interleukin-3 %%%fusion%%% %%%protein%%% versus granulocyte-macrophage colony-stimulating factor after autologous bone marrow transplantation for non-Hodgkin's lymphoma: results of a randomized double-blind trial.

5/6/10
09258988 97169053
Thrombospondin, a negative modulator of megakaryocytopoiesis. ? t s5/6/11-20

5/6/11
09249112 97051758
Human eosinophils express functional CD30 ligand and stimulate proliferation of a Hodgkin's disease cell line.

5/6/12
09237298 96343853
Differential expression of Fas (CD95) and Fas ligand on normal human phagocytes: implications for the regulation of apoptosis in neutrophils.

5/6/13
09227691 96223410
Phase I/II trial of PIXY321 to enhance engraftment following autologous bone marrow transplantation for lymphoid malignancy.

5/6/14
09225646 96200424
The effect of the %%%GM%%%-%%%CSF%%%/IL-3 %%%fusion%%% %%%protein%%% PIXY321 on bone marrow and circulating haemopoietic cells of previously untreated patients with cancer.

5/6/15
09205372 95355467
Signal transduction by a CD16/CD7/Jak2 %%%fusion%%% %%%protein%%%.

5/6/16
09178049 97449096
New understanding of the pathogenesis of CML: a prototype of early neoplasia.

5/6/17
09172020 97447239
Ricin fusion toxin targeted to the human granulocyte-macrophage colony stimulating factor receptor is selectively toxic to acute myeloid leukemia cells.

5/6/18
09163493 97387249
A recombinant %%%GM%%%-%%%CSF%%%-PE40 ligand toxin is functionally active but not cytotoxic to cells.

5/6/19
09101143 97353148
The signal transduction through Grb2/Ash in hematopoietic cells.

5/6/20
09042986 97284702
The kinase domain of Jak2 mediates induction of bcl-2 and delays cell death in hematopoietic cells.
? ds

Set Items Description
S1 2 (MAGE()3) AND (GMCSF OR GM()CSF)
S2 6643 (GMCSF OR GM()CSF)
S3 86 S2 AND FUSION()PROTEIN
S4 4 (GMCSF OR GM()CSF)(5N)(ANCHOR OR MEMBRANE()ATTACH? OR TRAN- SMEMBRANE)
S5 86 S3 NOT S4
S6 0 S5 AND ANCHOR?
? t s5/6/21-86

5/6/21
09040316 97246188
In vitro production of megakaryocytes from PIXY321 versus %%%GM%%%- %%%CSF%%%-mobilized peripheral blood progenitor cells.

5/6/22
09032817 96430277
C-kit ligand (SCF) in human multiple myeloma cells.

5/6/23
09007780 97261978
Purification and molecular cloning of SH2- and SH3-containing inositol polyphosphate-5-phosphatase, which is involved in the signaling pathway of granulocyte-macrophage colony-stimulating factor, erythropoietin, and Bcr-Abl.

5/6/24
08938349 97199402

The conserved lymphokine element-0 in the IL5 promoter binds to a high mobility group-1 protein.

5/6/25
08853869 97113340
A nine-amino acid peptide from IL-1beta augments antitumor immune responses induced by protein and DNA vaccines.

5/6/26
08843470 97102692
Regulation of the synthesis of bcl-2 protein by growth factors.

5/6/27
08782302 97054671
Exogenous and endogenous antigens are differentially presented by mast cells to CD4+ T lymphocytes.

5/6/28
08747851 96420633
Phase I trial of recombinant %%%fusion%%% %%%protein%%% PIXY321 for mobilization of peripheral-blood cells.

5/6/29
08717835 96071135
pIXY321 protects against Ara-C or taxol-induced apoptosis and loss of clonogenic survival of normal human bone marrow progenitor cells.

5/6/30
08693902 96376358
DNA immunization induces protective immunity against B-cell lymphoma.

5/6/31
08682066 96351963
Interleukins and colony stimulating factors in human myeloid leukemia cell lines.

5/6/32
08640391 96309626
Mechanism of transcriptional activation of the immediate early gene Egr-1 in response to PIXY321.

5/6/33
08596055 96247489
A phase II study of cyclophosphamide followed by PIXY321 as a means of mobilizing peripheral blood hematopoietic progenitor cells [published erratum appears in Exp Hematol 1997 Mar;25(3):270]

5/6/34
08581763 96203784
Prospective, randomized trial of 5-fluorouracil, leucovorin, doxorubicin, and cyclophosphamide chemotherapy in combination with the interleukin-3/granulocyte-macrophage colony-stimulating factor (%%%GM%%%- %%%CSF%%%) %%%fusion%%% %%%protein%%% (PIXY321) versus %%%GM%%%-%%%CSF%%% in patients with advanced breast cancer.

5/6/35
08571801 96200992
Expression of FLT3 receptor and response to FLT3 ligand by leukemic cells.

5/6/36
08569734 96194723
Early suppressive effects of chemotherapy and cytokine treatment on committed versus primitive haemopoietic progenitors in patient bone marrow.

5/6/37
08509016 96132719
The AML1/ETO %%%fusion%%% %%%protein%%% blocks transactivation of the %%%GM%%%-%%%CSF%%% promoter by AML1B.

5/6/38
08507116 96130277
Immunocytochemical analysis of tumor cells in pre- and post-culture peripheral blood progenitor cell collections from breast cancer patients.

5/6/39
08494343 96116885
Cytofluorimetric and functional analysis of c-kit receptor in acute leukemia.

5/6/40
08434579 96033074
Characteristic biological features of human megakaryoblastic leukaemia cell lines.

5/6/41
08418176 95385746
Flt3 ligand stimulates/costimulates the growth of myeloid stem/progenitor cells.

5/6/42
08412834 95256249
The proto-oncogene product c-Cbl becomes tyrosine phosphorylated by stimulation with %%%GM%%%-%%%CSF%%% or Epo and constitutively binds to the SH3 domain of Grb2/Ash in human hematopoietic cells.

5/6/43
08411657 95222300
Clinical applications of hematopoietic growth factors [see comments]

5/6/44
08409792 95137005
Tyrosine phosphorylation of p95Vav in myeloid cells is regulated by %%%GM%%%-%%%CSF%%% , IL-3 and steel factor and is constitutively increased by p210BCR/ABL [see comments]

5/6/45
08402600 95399776
A murine cytokine fusion toxin specifically targeting the murine granulocyte-macrophage colony-stimulating factor

(%%%GM%%%-%%%CSF%%%) receptor on normal committed bone marrow progenitor cells and %%%GM%%%-%%%CSF%%%-dependent tumor cells.

5/6/46
08393555 95387656
The acute promyelocytic leukemia-specific PML/RAR alpha %%%fusion%%% %%%protein%%% reduces the frequency of commitment to apoptosis upon growth factor deprivation of %%%GM%%%-%%%CSF%%%-dependent myeloid cells.

5/6/47
08324176 95293979
The amino-terminal portion of the JAK2 protein kinase is necessary for binding and phosphorylation of the granulocyte-macrophage colony-stimulating factor receptor beta c chain.

5/6/48
08271043 95204905
Induction of autoantibody responses to %%%GM%%%-%%%CSF%%% by hyperimmunization with an Id-%%%GM%%%-%%%CSF%%% %%%fusion%%% %%%protein%%%.

5/6/49
08270412 95203343
Effects of in vivo treatment with PIXY321 (%%%GM%%%-%%%CSF%%%/IL-3 %%%fusion%%% %%%protein%%%) on proliferation kinetics of bone marrow and blood myeloid progenitor cells in patients with sarcoma.

5/6/50
08242730 95268047
Primitive hematopoietic progenitor cells are present in peripheral blood autografts.

5/6/51
08228241 94374493
Characterization and quantitation of primitive hematopoietic progenitor cells present in peripheral blood autografts.

5/6/52
08187179 95268058
Cytokine-dependent ex vivo expansion of early subsets of CD34+ cord blood myeloid progenitors is enhanced by cord blood plasma, but expansion of the more mature subsets of progenitors is favored.

5/6/53
08186468 95210988
Granulocyte-colony stimulating factor, granulocyte-macrophage colony stimulating factor, PIXY-321, stem cell factor, interleukin-3, and interleukin-7: receptor binding and effects on clonogenic proliferation in acute lymphoblastic leukemia.

5/6/54
08186050 95195626
Enrichment of peripheral blood stem cells in a primate model following administration of a single dose of rh-IL-1 beta.

5/6/55
08183739 95118872
Expression and functional role of c-kit ligand (SCF) in human multiple myeloma cells.

5/6/56
08182496 95086205
Regulation of interleukin-11 protein and mRNA expression in neonatal and adult fibroblasts and endothelial cells.

5/6/57
08180995 95052644
Idiotype-cytokine fusion proteins as cancer vaccines. Relative efficacy of IL-2, IL-4, and granulocyte-macrophage colony-stimulating factor.

5/6/58
08174357 94289726
Expression of interleukin-1 beta gene in candidate human hematopoietic stem cells.

5/6/59
08172146 94238907
Mast cell growth factor (c-kit ligand) restores growth of multipotent progenitors in myelodysplastic syndrome.

5/6/60
08171352 94220683
Thy-1 expression is linked to functional properties of primitive hematopoietic progenitor cells from human umbilical cord blood.

5/6/61
08133699 95180241
Potential role of granulocyte-macrophage colony-stimulating factor as vaccine adjuvant.

5/6/62
08109035 95135335
Expression of a biologically active human granulocyte-macrophage colony stimulating factor %%%fusion%%% %%%protein%%% in Escherichia coli.

5/6/63
07990666 94355911
PIXY321 (%%%GM%%%-%%%CSF%%%/IL-3 %%%fusion%%% %%%protein%%%): biology and early clinical development.

5/6/64
07889300 94201787
Effects of PIXY321, a granulocyte-macrophage colony-stimulating factor/interleukin-3 %%%fusion%%% %%%protein%%% , on chemotherapy-induced multilineage myelosuppression in patients with sarcoma.

5/6/65
07812523 93244623
Effect of hemopoietic growth factors G-CSF and pIXY 321 on the activity of high dose Ara-C in human myeloid leukemia cells.

5/6/66
07806268 94154609
c-kit ligand augments granulocyte-macrophage colony growth from patients with 5q- syndrome.

5/6/67
07803969 94083894
Cytotoxicity of a recombinant diphtheria toxin-granulocyte colony-stimulating factor %%%fusion%%% %%%protein%%% on human leukemic blast cells.

5/6/68
07800297 94009450
Increase in peripheral blood megakaryocyte progenitors following cancer therapy with high-dose cyclophosphamide and hematopoietic growth factors.

5/6/69
07796045 93307458
Modulation of the activity of a human granulocyte-macrophage colony-stimulating factor/interleukin-3 %%%fusion%%% %%%protein%%% (pIXY 321) by the macrocyclic lactone protein kinase C activator bryostatin 1.

5/6/70
07794965 93283672
Cytokine-induced selective expansion and maturation of erythroid versus myeloid progenitors from purified cord blood precursor cells.

5/6/71
07747966 94191166
Modulation by bryostatin 1 of the in vitro radioprotective effects of the %%%GM%%%-%%%CSF%%%/IL-3 %%%fusion%%% %%%protein%%% , PIXY 321, on normal human myeloid progenitors.

5/6/72
07712747 94107629
Retinoid receptors and acute promyelocytic leukaemia.

5/6/73
07644237 94009432
The effects of treatment with PIXY321 (%%%GM%%%-%%%CSF%%%/IL-3 %%%fusion%%% %%%protein%%%) on human polymorphonuclear leukocyte function.

5/6/74
07637902 94000569
PIXY 321 (%%%GM%%%-%%%CSF%%%/IL-3 %%%fusion%%% %%%protein%%%).

5/6/75
07618238 93386061
A %%%GM%%%-%%%CSF%%%/IL-3 %%%fusion%%% %%%protein%%% promotes neutrophil and platelet recovery in sublethally irradiated rhesus monkeys.

5/6/76
07520431 93226047
Idiotype/granulocyte-macrophage colony-stimulating factor %%%fusion%%% %%%protein%%% as a vaccine for B-cell lymphoma [see comments]

5/6/77
07387193 93081792
Granulocyte-macrophage colony-stimulating factor/interleukin-3 %%%fusion%%% %%%protein%%% (pIXY 321) enhances high-dose Ara-C-induced programmed cell death or apoptosis in human myeloid leukemia cells.

5/6/78
07340860 92324291
GMP-140 (P-selectin/CD62) binds to chronically stimulated but not resting CD4+ T lymphocytes and regulates their production of proinflammatory cytokines.

5/6/79
07338373 92267123
Ex vivo expansion of peripheral blood progenitor cells with recombinant cytokines.

5/6/80
07337089 92233922
Recombinant %%%GM%%%-%%%CSF%%%/IL-3 %%%fusion%%% %%%protein%%% : its effect on in vitro human megakaryocytopoiesis.

5/6/81
07334503 92119283
Role of c-kit ligand in the expansion of human hematopoietic progenitor cells.

5/6/82
07002795 91311304
CD45 cell surface antigens are linked to stimulation of early human myeloid progenitor cells by interleukin 3 (IL-3), granulocyte/macrophage colony-stimulating factor (%%%GM%%%-%%%CSF%%%), a %%%GM%%%-%%%CSF%%%/IL-3 %%%fusion%%% %%%protein%%%, and mast cell growth factor (a c-kit ligand).

5/6/83
06923839 91288552
Enhanced hematopoietic activity of a human granulocyte/macrophage colony-stimulating factor-interleukin 3 %%%fusion%%% %%%protein%%%.

5/6/84
06870494 92121667
Hybrid cytokines as hematopoietic growth factors.

5/6/85
06692943 91199046
Hematopoietic effects of a granulocyte-macrophage colony-stimulating factor/interleukin-3 %%%fusion%%% %%%protein%%%.

5/6/86
06224722 89193299
E. coli derived human granulocyte-macrophage colony-stimulating factor (rh %%%GM%%%-%%%CSF%%%) available for clinical trials.
? t s5/6/1-10t s5/3,ab/57

>>>'10T' not recognized as item list
? t s5/3,ab/57

5/3,AB/57
DIALOG(R)File 155:MEDLINE(R)

08180995 95052644
Idiotype-cytokine fusion proteins as cancer vaccines. Relative efficacy of IL-2, IL-4, and granulocyte-macrophage colony-stimulating factor. Chen TT; Tao MH; Levy R
Department of Medicine, School of Medicine, Stanford University, CA 94305.
J Immunol (UNITED STATES) Nov 15 1994, 153 (10) p4775-87, ISSN 0022-1767 Journal Code: IFB
Contract/Grant No.: CA33399, CA, NCI; GM07365, GM, NIGMS Languages: ENGLISH
Document type: JOURNAL ARTICLE
Idiotypic determinants, antigenic sites expressed on the variable region of Ig molecules of malignant B cells, represent tumor-specific Ags but are weak immunogens. We have previously shown that the immunogenicity can be dramatically increased by fusing tumor Id to granulocyte macrophage (%%%GM%%%)-%%%CSF%%%. Here, we demonstrate that fusion proteins with IL-2 or IL-4 can also be highly immunogenic. Co-immunization of these fusion proteins with another Id demonstrated the importance of physical linkage between the cytokine and relevant Ag for this enhancement. All three fusion proteins are capable of eliciting significant levels of specific Abs against the Id without the use of carrier proteins or adjuvants, although the %%%GM%%%-%%%CSF%%% %%%fusion%%% %%%protein%%% appeared to be unique in its ability to induce higher titers of anti-Id Abs in the primary response. Furthermore, the Id-IL-2 %%%fusion%%% %%%protein%%% induced high titers of IgG2a and IgG3 anti-Id Abs, whereas the Id-IL-4 and Id-%%%GM%%%-%%%CSF%%% fusion proteins did not. Despite the differences, tumor protection was comparable in all mice having significant titers of anti-Id Abs, regardless of the %%%fusion%%% %%%protein%%% used. We concluded that Id-cytokine fusion proteins are potent immunogens that can elicit significant antitumor immunity. The general approach of fusing a cytokine to a potential Ag may be applicable to the design of vaccines for immunotherapy of other types of tumors as well as for other pathogens and disease states.
? b 5

06aug98 16:24:59 User217743 Session D451.4
$6.00 2.000 DialUnits File155
$0.00 86 Type(s) in Format 6
$1.40 7 Type(s) in Format 4 (UDF)
$1.40 93 Types
$7.40 Estimated cost File155
$7.40 Estimated cost this search
$9.40 Estimated total session cost 4.257 DialUnits
File 5:BIOSIS PREVIEWS(R) 1969-1998/JUL W4
(c) 1998 BIOSIS

Set Items Description
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? s (gmcsf or gm()csf)(5n)(anchor or membrane()attach? or transmembrane)
295 GMCSF
20946 GM
32963 CSF
7575 GM(W)CSF
4324 ANCHOR
409735 MEMBRANE
63441 ATTACH?
651 MEMBRANE(W)ATTACH?
26273 TRANSMEMBRANE
S1 6 (GMCSF OR GM()CSF)(5N)(ANCHOR OR MEMBRANE()ATTACH? OR TRANSMEMBRANE)
? t s1/3,ab/all

1/3,AB/1
DIALOG(R)File 5:BIOSIS PREVIEWS(R)

13547296 BIOSIS Number: 99547296
Oligomerization of the soluble granulocyte-macrophage colony-stimulating factor receptor: Identification of the functional ligand-binding species Brown C B; Pihl C E; Murray E W
Room 2880, Health Sci. Center, Univ. Calgary, 3330 Hosp. Drive N.W. Calgary, AB T2N 4N1, Canada
Cytokine 9 (4). 1997. 219-225.
Full Journal Title: Cytokine
ISSN: 1043-4666
Language: ENGLISH
Print Number: Biological Abstracts Vol. 103 Iss. 012 Ref. 170724 The ligand-specific alpha subunit of the dimeric human %%%GM%%%-%%%CSF%%% receptor exists in both %%%transmembrane%%% anchored (tmGM-CSFR-alpha) and soluble (sGM-CSFR-alpha) isoforms. sGM-CSFR-alpha binds to GM-CSF in solution and antagonizes GM-CSF biological activity in vitro. In an effort to better understand the biological properties of sGM-CSFR-alpha the authors have attempted to define the exact stoichiometry of the interaction between GM-CSF and sGM-CSFR-alpha. Size separation of sGM-CSFR-alpha by polyacrylamide gel electrophoresis (PAGE) under non-reducing conditions demonstrated that sGM-CSFR-alpha can exist in solution not only in a monomeric state but also in higher order oligomers. FPLC analvsis of ligand/sGM-CSFR-alpha complexes suggested that only one of these sGM-CSFR-alpha species could functionally bind GM-CSF. PAGE analysis of FPLC fractions demonstrated that the peak of GM-CSF binding activity corresponded to the presence of a monomeric form of sGM-CSFR-alpha. The experiments demonstrate that while sGM-CSFR-alpha can adopt oligomeric forms in solution, the binding of GM-CSF to sGM-CSFR-alpha most likely occurs in a (GM-CSF)-1 (sGM-CSFR-alpha)-1 configuration.

1/3,AB/2
DIALOG(R)File 5:BIOSIS PREVIEWS(R)

13084059 BIOSIS Number: 99084059
Ligand-independent cell surface expression of the human soluble granulocyte-macrophage colony-stimulating factor receptor alpha subunit depends on co-expression of the membrane-associated receptor beta subunit Murray E W; Pihl C; Morcos A; Brown C B
Dep. Med., Health Sci. Cent., 3330 Hospital Dr. NW., Univ. Calgary, Calgary, AB T2N 4N1, Canada
Journal of Biological Chemistry 271 (26). 1996. 15330-15335. Full Journal Title: Journal of Biological Chemistry
ISSN: 0021-9258
Language: ENGLISH
Print Number: Biological Abstracts Vol. 102 Iss. 004 Ref. 049508 The hematopoietic cytokine granulocyte-macrophage colony-stimulating factor (GM-CSF) mediates its activity through binding to cell surface

receptors. The receptor for GM-CSF belongs to a superfamily of cytokine receptors characterized by a conserved extracellular motif. The high affinity %%%GM%%%-%%%CSF%%% receptor (GMR) consists of two %%%transmembrane%%% anchored subunits; a ligand binding a subunit (transmembrane GMR-alpha) and a signal transducing beta subunit (GMR-beta), both of which belong to the cytokine receptor superfamily. The human GM-CSF receptor a subunit also exists in a soluble form (solGMR-alpha), which antagonizes GM-CSF activity in vitro. We directly tested the potential for solGMR-alpha to interact with GMR-beta in vitro. Our experiments demonstrated that exogenous solGMR-alpha, even in the presence of GM-CSF, does not interact with GMR-beta on the cell surface. However, when solGMR-alpha and GMR-beta are co-expressed in baby hamster kidney cells, solGMR-alpha is retained on the cell surface and forms a functional intermediate affinity GM-CSF binding complex (K-d = 331 pm). In addition, the cell surface expression of solGMR-alpha is independent of the presence of GM-CSF as demonstrated using flow cytometry. Cells expressing only solGMR-alpha do not show cell surface retention or form functional GM-CSF cell surface binding complexes. Sequencing of our GMR-beta clone revealed a nucleotide substitution (A fwdarw C) resulting in the substitution of Ala for Glu at position 9 from the amino terminus of the mature GMR-beta peptide. Because the GMR-beta (A fwdarw C) clone is capable of forming functional high affinity receptors with transmembrane GMR-alpha (K-d = 64 pM), we feel that the cell surface retention of solGMR-alpha is independent of the GMR-beta mutation. We suggest that the co-expression and interaction of solGMR-alpha and GMR-beta represents a previously unrecognized GM-CSF receptor complex and a novel, ligand-independent mechanism of cytokine receptor assembly.

1/3,AB/3
DIALOG(R)File 5:BIOSIS PREVIEWS(R)

11616531 BIOSIS Number: 98216531
In vitro characterization of the human recombinant soluble granulocyte-macrophage colony-stimulating factor receptor
Brown C B; Beaudry P; Laing T D; Shoemaker S; Kaushansky K Room 2880, Health Sci. Cent., Univ. Calgary, 3330 Hospital Dr. NW, Calgary, Alberta T2N 4N1, Canada
Blood 85 (6). 1995. 1488-1495.
Full Journal Title: Blood
ISSN: 0006-4971
Language: ENGLISH
Print Number: Biological Abstracts Vol. 099 Iss. 010 Ref. 138707
We have cloned, expressed, and partially purified a naturally occurring, truncated, soluble form of the human granulocyte-macrophage-stimulating factor (GM-CSF) receptor alpha subunit to investigate its biochemical and biologic properties. The soluble receptor species lacks the transmembrane and cytoplasmic domains that are presumably removed from the Intact receptor cDNA by a mechanism of alternative splicing. The resulting soluble 55- to 60-kD glycosylated receptor species binds GM-CSF with a dissociation constant (kd) of 3.8 nmol/l. The soluble GM-CSF receptor successfully competes for %%%GM%%%-%%%CSF%%% binding not only with the %%%transmembrane%%%-anchored %%%GM%%%-%%%CSF%%% receptor a subunit but also with the native oligomeric high-affinity receptor complex. In addition, in human bone marrow colony-forming assays, the soluble GM-CSF receptor species can antagonize the activity of GM-CSF. Our data suggest that the soluble GM-CSF receptor may be capable of acting in vivo as a modulator of the biologic activity of GM-CSF.

1/3,AB/4
DIALOG(R)File 5:BIOSIS PREVIEWS(R)

7312733 BIOSIS Number: 38093254
%%%GM%%%-%%%CSF%%% RECEPTOR STRUCTURE AND %%%TRANSMEMBRANE%%% SIGNALING
DIPERSIO J F; GOLDE D W; GASSON J D
11-640 FACTOR BUILDING, DIV. HEMATOL.-ONCOL., DEP. MED., UCLA MED. CENTER, LOS ANGELES, CALIF. 90024.
SYMPOSIUM ON BLOOD CELL GROWTH FACTORS: THEIR BIOLOGY AND CLINICAL APPLICATIONS HELD AT THE SECOND INTERNATIONAL CAPRI CONFERENCE, CAPRI, ITALY, OCTOBER 8-12, 1989. INT J CELL CLONING 8 (SUPPL. 1). 1990. 63-75. CODEN: IJCCE
Language: ENGLISH
Document Type: CONFERENCE PAPER

1/3,AB/5
DIALOG(R)File 5:BIOSIS PREVIEWS(R)

7099816 BIOSIS Number: 88022561
EFFECTS OF RECOMBINANT HUMAN GRANULOCYTE-MACROPHAGE COLONY-STIMULATING FACTOR %%%GM%%%-%%%CSF%%%-R-H ON %%%TRANSMEMBRANE%%% ELECTRICAL POTENTIALS IN GRANULOCYTES RELATIONSHIP BETWEEN ENHANCEMENT OF LIGAND-MEDIATED DEPOLARIZATION AND AUGMENTATION OF SUPEROXIDE ANION PRODUCTION
SULLIVAN R; FREDETTE J P; LEAVITT J L; GADENNE A-S; GRIFFIN J D; SIMONS E R
HEMATOL. SECT., DEP. OF MED., BOSTON UNIV. MED. SCH., BOSTON, MASS.
J CELL PHYSIOL 139 (2). 1989. 361-369. CODEN: JCLLA
Full Journal Title: Journal of Cellular Physiology
Language: ENGLISH
When human granulocytes that have been primed with recombinant human granulocyte-macrophage colony-stimulating factor (GM-CSFrh) are activated by ligands that stimulate the respiratory burst, the amount of superoxide anion (O2-) they generate is significantly increased. We have found that the accelerated rate of O2- release occurring under these conditions is accompanied by an antecedent increase in membrane depolarization. We examined the nature of the enhancement of membrane depolarization in GM-CSFrh-primed granulocytes and investigated its relationship to the increase in O2- generation by N-formyl methionylleucylphenylalanine (fMLP)-activated granulocytes. We found that augmented depolarization could not be accounted for by a change in the resting membrane potential induced by growth factor and was still present after either blocking passive transmembrane Na+ movement with dimethylamiloride or by increasing the membrane's permeability to K+ with valinomycin. When their ability to depolarize was virtually eliminated by dissipating the transmembrane K+ gradient, GM-CSFrh-pretreated cells continued to generate more O2- after fMLP than did control cells. These results indicate that augmentation of the granulocyte's ability to generate O2- anions, which is induced by priming with GM-CSFrh, is independent both of

the resting transmembrane potential and of alterations in the extent of membrane potential change induced by stimuli such as fMLP.

1/3,AB/6
DIALOG(R)File 5:BIOSIS PREVIEWS(R)
(c) 1998 BIOSIS. All rts. reserv.

6188962 BIOSIS Number: 35054483
HUMAN %%%GM%%%-%%%CSF%%% RECEPTOR BINDING AND %%%TRANSMEMBRANE%%% SIGNALLING
DIPERSIO J; BILLING P; KAUFMAN S; NACCACHE P; BORGEAT P; GASSON J DIV. HEMATOL.-ONCOL., UCLA SCH. MED., LOS ANGELES, CALIF. SYMPOSIUM ON GROWTH FACTORS AND THEIR RECEPTORS: GENETIC CONTROL AND RATIONAL APPLICATION HELD AT THE 17TH ANNUAL MEETING OF THE UCLA (UNIVERSITY OF CALIFORNIA-LOS ANGELES) SYMPOSIA ON MOLECULAR AND CELLULAR BIOLOGY, KEYSTONE, COLORADO, USA, JANUARY 24-30, 1988. J CELL BIOCHEM SUPPL 0 (12 PART A). 1988. 90. CODEN: JCBSD
Language: ENGLISH
Document Type: CONFERENCE PAPER
? s (gmcsf or gm()csf)

295 GMCSF
20946 GM
32963 CSF
7575 GM(W)CSF
S2 7744 (GMCSF OR GM()CSF)
? s s2 and fusion()protein

7744 S2
53154 FUSION
998884 PROTEIN
9339 FUSION(W)PROTEIN
S3 89 S2 AND FUSION()PROTEIN
? s s3 not (gmcsf or gm()csf)()receptor

89 S3
295 GMCSF
20946 GM
32963 CSF
7575 GM(W)CSF
373966 RECEPTOR
306 (GMCSF OR GM(W)CSF)(W)RECEPTOR
S4 81 S3 NOT (GMCSF OR GM()CSF)()RECEPTOR
? s s4 and membrane

81 S4
409735 MEMBRANE
S5 2 S4 AND MEMBRANE
? t s5/3,ab/1,2

5/3,AB/1
DIALOG(R)File 5:BIOSIS PREVIEWS(R)
(c) 1998 BIOSIS. All rts. reserv.

13564242 BIOSIS Number: 99564242
The kinase domain of Jak2 mediates induction of Bcl-2 and delays cell death in hematopoietic cells
Sakai I; Kraft A S
Div. Med. Oncol., Dep. Med., Univ. Colorado Health Sci. Cent., Denver, CO 80262, USA
Journal of Biological Chemistry 272 (19). 1997. 12350-12358. Full Journal Title: Journal of Biological Chemistry
ISSN: 0021-9258
Language: ENGLISH
Print Number: Biological Abstracts Vol. 104 Iss. 001 Ref. 005092 Granulocyte-macrophage colony-stimulating factor (%%%GM%%%-%%%CSF%%%), interleukin (IL)-3, and IL-5 stimulate DNA synthesis and proliferation and inhibit apoptosis in hematopoietic cells. Multiple signal pathways are activated by binding of these ligands to their receptors, which share a common beta subunit. Janus protein kinase 2 (Jak2) binds to the %%%membrane%%% proximal domain of the chain and is phosphorylated on receptor ligation. To explore the role of Jak2 in the regulation of specific signal transduction pathways, we constructed fusion proteins with a CD 16 external domain, a CD7 transmembrane region, and a Jak2 cytoplasmic domain. This cytoplasmic domain consisted either of wild type Jak2 (CD16/Jak2-W) or Jak2 mutations with deletions of (a) the amino terminus (CD16/Jak2-N), (b) kinase-like domain (CD16/Jak2-B), (c) kinase domain (CD16/Jak2-C), or (d) amino-terminal and kinase-like domains, leaving the kinase domain (CD16/Jak-K) intact. In contrast to the CD16/Jak2-W %%%fusion%%% %%%protein%%% , which requires crosslinking for activation, CD16/Jak2-N, CD16/JaK2-B, and CD16/Jak2-K were constitutively phosphorylated, and they stimulated Shc phosphorylation and increased binding of STAT to DNA in Ba/F3 cells. Cell lines derived from IL-3-dependent Ba/F3 cells stably transfected with CD16/Jak2-W, CD16/Jak2-N, or CD16/Jak2-B mammalian expression vectors died at a rate similar to that of the parental cells on IL-3 deprivation. In contrast, CD16/Jak2-K cell lines exhibited increased expression of bcl-2 and pim-1 MRNA and maintained their viability when compared with control cell lines. Thus, activation of tyrosine phosphorylation by creating a CD16/Jak2-K fusion is sufficient to activate pathways that prevent cell death.

5/3,AB/2
DIALOG(R)File 5:BIOSIS PREVIEWS(R)
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9568860 BIOSIS Number: 94073860
GMP-140 P-SELECTIN-CD62 BINDS TO CHRONICALLY STIMULATED BUT NOT RESTING CD4 POSITIVE T LYMPHOCYTES AND REGULATES THEIR PRODUCTION OF PROINFLAMMATORY CYTOKINES
DAMLE N K; KLUSSMAN K; DIETSCH M T; MOHAGHEGHPOUR N; ARUFFO A BRISTOL-MYERS SQUIBB PHARMCEUTICAL RES. INST., 3005 FIRST AVE., SEATTLE, WASH. 98121.
EUR J IMMUNOL 22 (7). 1992. 1789-1793. CODEN: EJIMA
Full Journal Title: European Journal of Immunology
Language: ENGLISH
GMP-140 (P-selectin), a 140-kDa granular %%%membrane%%% glycoprotein localized to the .alpha.-granules of platelets and the Weibel-Palade bodies of endothelial cells, is thought to play an important role in adhesive interactions predominantly between granulocytes, platelets and vascular endothelial cells during inflammation. Although GMP-140 binds to granulocytes, its binding to lymphocytes has not been demonstrated. Using genetically engineered IgG C.gamma.1 %%%fusion%%% %%%protein%%% of the extracellular domains of GMP-140, we demonstrate that GMP-140 binds to chronically antigen (Ag)-stimulated CD4+ T cells. Freshly isolated CD4+ T cells did not bind GMP-140, but priming and subsequent stimulation with alloantigen induced and gradually increased

expression of GMP-140-reactive structures on their surface. T cells isolated from rheumatoid synovial fluids also exhibited strong binding to GMP-140. The binding of GMP-140 to primed T cells is not influenced by preactivation with phorbol 12-myristate 13-acetate, is almost completely abolished by pretreatment of T cells with neuraminidase or trypsin, and is also strongly inhibited by EDTA, the soluble sulfated glycans dextran sulfate, fucoidan, and heparin, but not by chondroitin sulfates. In spite of its strong binding to Ag-primed T cells, GMP-140 did not modulate the proliferative responses of these cells to various stimuli. However, GMP-140 in conjunction with anti-T cell receptor .alpha..beta. monoclonal antibodies augmented the production of granulocyte-macrophage colony-stimulating factor %%%GM%%%-%%%CSF%%% and inhibited the production of interleukin-8 by Ag-primed T cells without influencing their tumor necrosis factor-.alpha. production. These results suggest that GMP-140 binds to chronically stimulated CD4+T cells and differentially modulates their production of proinflammatory cytokines. The ability of Ag-primed T cells to bind GMP-140 may facilitate interactions with activated platelets and endothelial cells affecting the course of inflammation.

? s (MAGE()3) AND (GMCSF OR GM()CSF)

```
        261 MAGE
    1672009 3
         82 MAGE(W)3
        295 GMCSF
      20946 GM
      32963 CSF
       7575 GM(W)CSF
 S6       4 (MAGE()3) AND (GMCSF OR GM()CSF)
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? t s6/3,ab/all

6/3,AB/1
DIALOG(R)File 5:BIOSIS PREVIEWS(R)
(c) 1998 BIOSIS. All rts. reserv.

14068110 BIOSIS Number: 01068110
Transfer of tumor-associated antigen genes into dendritic cells for active immunotherapy of neoplastic diseases
Russo V; Sartirana C; Dalebra P; Rossini S; Traversari C; Bordignon C Ist. Sci. H.S. Raffaele, Milano, Italy
Blood 90 (10 SUPPL. 1 PART 1). 1997. 405A.
Full Journal Title: 39th Annual Meeting of the American Society of Hematology, San Diego, California, USA, December 5-9, 1997. Blood ISSN: 0006-4971
Language: ENGLISH
Document Type: CONFERENCE PAPER
Print Number: Biological Abstracts/RRM Vol. 050 Iss. 002 Ref. 030518

6/3,AB/2
DIALOG(R)File 5:BIOSIS PREVIEWS(R)
(c) 1998 BIOSIS. All rts. reserv.

13814699 BIOSIS Number: 99814699
Transfection of IL-2 augments CTL response to human melanoma cells in vitro: Immunological characterization of a melanoma vaccine Van Elsas A; Aarnoudse C; Van Der Minne C E; Van Der Spek C W; Brouwenstijn A; Osanto S; Schrier P I
Dep. Clinical Oncol., Univ. Hosp., P.O. Box 9600, 2300 RC Leiden, Netherlands
Journal of Immunotherapy 20 (5). 1997. 343-353.
Full Journal Title: Journal of Immunotherapy
ISSN: *********
Language: ENGLISH
Print Number: Biological Abstracts Vol. 104 Iss. 012 Ref. 172303 We have transfected human melanoma cell line 518A2 with the cDNA encoding interleukin-2 (IL-2) or granulocyte-macrophage colony-stimulating factor (%%%GM%%%-%%%CSF%%%), and compared cytokine-producing clones for their ability to induce melanoma-specific cytotoxic T lymphocytes (CTL) from autologous peripheral blood mononuclear cells (PBMC) in vitro. The parental cell line expressed HLA-A1, HLA-A2, ICAM-1, LFA-3, in addition to the common CTL antigens MAGE-1, %%%MAGE%%%-%%%3%%% , tyrosinase, gp100, and Melan-A/MART-1. Stimulation of autologous PBMC responders with the IL-2-transfected clone 518/IL2.14 specifically induced CTL lines reactive with all cell lines derived from the autologous patient. Strikingly, %%%GM%%%-%%%CSF%%% -transfected 518A2 cells did not induce anti-tumor CTL reactivity. CTL induction against 518/ IL2.14 was independent of HLA class II expression or CD4 help. The parental cell line 518A2 gained immunogenic properties when high concentrations of IL-2 were supplied exogenously, indicating that IL-2 produced and present at high levels locally by itself enhanced immunogenicity. From the autologous CTL line reactive with 518/ IL2.14, clones were generated against an as yet unknown antigen, which was present in all autologous melanoma cell lines as well as in 7 of 15 HLA-A2+ melanoma cell lines tested, but not in melanocytes. These results will be discussed with respect to the possibility of using IL-2-transfected melanoma cells as a vaccine for treatment of patients with melanoma.

6/3,AB/3
DIALOG(R)File 5:BIOSIS PREVIEWS(R)
(c) 1998 BIOSIS. All rts. reserv.

13533636 BIOSIS Number: 99533636
Induction of peptide specific lymphocytes using peptide-pulsed cultured dendritic cells from patient with HLA-A2 and %%%MAGE%%%-%%%3%%% esophageal cancer cell line
Yamasaki S; Okino T; Li L; Kanaoka S; Shimada Y; Imamura M First Dep. Surgery, Kyoto Univ., Kyoto 606, Japan
Proceedings of the American Association for Cancer Research Annual Meeting 38 (0). 1997. 631.
Full Journal Title: Eighty-eighth Annual Meeting of the American Association for Cancer Research, San Diego, California, USA, April 12-16, 1997. Proceedings of the American Association for Cancer Research Annual Meeting
ISSN: 0197-016X
Language: ENGLISH
Document Type: CONFERENCE PAPER
Print Number: Biological Abstracts/RRM Vol. 049 Iss. 006 Ref. 098416

6/3,AB/4
DIALOG(R)File 5:BIOSIS PREVIEWS(R)
(c) 1998 BIOSIS. All rts. reserv.

13249289 BIOSIS Number: 99249289
Induction of antigen-specific tumor immunity by genetic and cellular vaccines against MAGE: Enhanced tumor protection by coexpression of granulocyte-macrophage colony-stimulating factor and B7-1
Bueler H; Mulligan R C
Howard Hughes Medical Inst., Children's Hosp., Harvard Medical Sch., 300 Longwood Ave., Boston, MA 02115, USA
Molecular Medicine (Cambridge) 2 (5). 1996. 545-555.
Full Journal Title: Molecular Medicine (Cambridge)
ISSN: 1076-1551

Language: ENGLISH
Print Number: Biological Abstracts Vol. 102 Iss. 011 Ref. 164919 Background: A number of tumors express antigens that are recognized by specific cytotoxic T cells. The normal host immune responses, however, are not usually sufficient to cause tumor rejection. Using appropriate immunization strategies, tumor-specific antigens may serve as targets against which tumor-destructive immune responses can be generated. MAGE-1 and %%%MAGE%%%-%%%3%%% are two clinically relevant antigens expressed in many human melanomas and other tumors, but not in normal tissues, except testis. Here, we have investigated whether DNA and cellular vaccines against MAGE-1 and %%%MAGE%%%-%%%3%%% can induce antigen-specific anti-tumor immunity and cause rejection of MAGE-expressing tumors. Materials and Methods: Mice were immunized against MAGE-1 and %%%MAGE%%%-%%%3%%% by subcutaneous injection of genetically modified embryonic fibroblasts or intramuscular injection of purified DNA. Mice were injected with lethal doses of B16 melanoma cells expressing the corresponding MAGE antigens or the unrelated protein SIV tat, and tumor development and survival were monitored. Results: Intramuscular expression of MAGE-1 and %%%MAGE%%%-%%%3%%% by plasmid DNA injection and subcutaneous immunization with syngeneic mouse embryonic fibroblasts transduced with recombinant retroviruses to express these antigens induced specific immunity against tumors expressing MAGE-1 and %%%MAGE%%%-%%%3%%%. Both CD4+ and CD8+ T cells were required for anti-tumor immunity. Coexpression of granulocyte-macrophage colony stimulating factor (%%%GM%%%-%%%CSF%%%) or B7-1 significantly increased anti-tumor immunity in an antigen-specific manner and resulted in a considerable proportion of mice surviving lethal tumor challenge. Conclusions: Our results suggest that genetic and cellular vaccines against MAGE and other tumor antigens may be useful for the therapy of tumors expressing specific markers, and that %%%GM%%%-%%%CSF%%% and B7-1 are potent stimulators for the induction of antigen-specific tumor immunity.
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$11.60 8 Type(s) in Format 5 (UDF)
$17.40 12 Types
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$22.65 Estimated cost this search
$32.05 Estimated total session cost 5.257 DialUnits
File 351:DERWENT WPI
1963-1998/UD=9830;UP=9827;UM=9825
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*File 351: All images are now present. The display formats have changed for 1998. See HELP FORM 351 for more information.

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2761756 3
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11 GMCSF
3208 GM
1150 CSF
285 GM(W)CSF
S1 1 (MAGE()3) AND (GMCSF OR GM()CSF)
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WPI Acc No: 98-159456/199814
XRAM Acc No: C98-051477
Treatment or prevention of melanoma - using melanoma cells expressing shared immuno-dominant antigen and modified for increased expression of a cytokine to improve immunogenicity
Patent Assignee: UNIV JOHNS HOPKINS SCHOOL MEDICINE (UYJO); US DEPT HEALTH & HUMAN SERVICES (USSH)
Inventor: ADLER A; JAFFEE E M; PARDOLL D M; ROSENBERG S A; TOPALIAN S L Number of Countries: 077 Number of Patents: 002
Patent Family:
Patent No Kind Date Applicat No Kind Date Main IPC Week WO-9806746 A2 19980219 97WO-US12868 A 19970804 C07K-014/00 199814 B AU-9738899 A 19980306 97AU-0038899 A 19970804 C07K-014/00 199830 E
Priority Applications (No Type Date): 96US-0024098 A 19960816 Patent Details:
Patent Kind Lan Pg Filing Notes Application Patent WO-9806746 A2 E 27
Designated States (National): AL AM AT AU AZ BA BB BG BR BY CA CH CN CU CZ DE DK EE ES FI GB GE GH HU IL IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MD MG MK MN MW MX NO NZ PL PT RO RU SD SE SG SI SK SL TJ TM TR TT UA UG UZ VN YU ZW
Designated States (Regional): AT BE CH DE DK EA ES FI FR GB GH GR IE IT KE LS LU MC MW NL OA PT SD SE SZ UG ZW
AU-9738899 A Based on WO-9806746
Abstract (Basic): WO 9806746 A
Treatment or prevention of melanoma comprises (a) modifying a melanoma cell line (A) that expresses at least 1 shared immunodominant melanoma antigen (Ag) so that it produces increased levels of a cytokine (I) and (b) administering the modified cell to a mammal at risk of developing melanoma.
(A) are allogeneic and not MHC matched to the patient. Ag are melanocyte-specific differentiation or tumour-specific shared antigens, and particularly at least 3 Ag are expressed. Most preferably the cells express %%%MAGE%%%-%%%3%%%, tyrosinase, MART-1/Melan-A, gp75 and gp100. Specified cell lines are 526-MEL and 624-MEL. Before administration, the cells are irradiated (typically at 10-30 kRad) and treated, by genetic manipulation to increase (I) production, or by formulating with non-specific adjuvants, to increase immunogenicity. Specifically (I) is granulocyte macrophage colony-stimulating factor (%%%GM%%%-%%%CSF%%%) and the gene encoding it is introduced using a conventional vector or as naked DNA, optionally under control of a melanocyte-specific or inducible promoter. Preferably the modified cells express over 36 ng (I)/million cells/day.
USE - The cells are administered by injection or inhalation, particularly subcutaneous or intradermal injection at 106-109 cells. They may be administered before, or in combination with, immunotherapy or other (e.g. surgical) methods of treatment.
ADVANTAGE - The modified cells provide a melanoma vaccine without requiring autologous or MHC (major

histocompatibility complex)-matched tumour cells. The use of shared antigens means that the vaccine will be effective in many different patients. Increasing the expression of (I) improves the immunogenicity of the cells. Since Ag are also expressed by some non-melanoma cancers (e.g. small cell lung cancer, colon and breast cancers), these may also be treated or prevented with the modified cells.
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Title Terms: TREAT; PREVENT; MELANOMA; MELANOMA; CELL; EXPRESS; SHARE; IMMUNO; DOMINANT; ANTIGEN; MODIFIED; INCREASE; EXPRESS; CYTOKINE; IMPROVE ; IMMUNOGENIC
Derwent Class: B04; D16
International Patent Class (Main): C07K-014/00
File Segment: CPI
Manual Codes (CPI/A-N): B04-F02; B14-S11C; D05-H07; D05-H08; D05-H09; D05-H10
Chemical Fragment Codes (M1):
01 M423 M781 M903 N135 P633 Q233 V288 V754
? b 34

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$13.10 Estimated cost File351
$13.10 Estimated cost this search
$45.15 Estimated total session cost 6.257 DialUnits
File 34:SciSearch(R) Cited Ref Sci 1990-1998/Jul W4
(c) 1998 Inst for Sci Info

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315 GMCSF
13908 GM
22925 CSF
7658 GM(W)CSF
S1 6 (MAGE()3) AND (GMCSF OR GM()CSF)
? t s1/3,ab/all

1/3,AB/1
DIALOG(R)File 34:SciSearch(R) Cited Ref Sci
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06351537 Genuine Article#: YL383 Number of References: 191 Title: The molecular basis of cancer immunotherapy by cytotoxic T lymphocytes
Author(s): Lindauer M; Stanislawski T; Haussler A; Antunes E; Cellary A; Huber C; Theobald M (REPRINT)
Corporate Source: UNIV MAINZ,MED KLIN 3, DEPT HEMATOL, LANGENBECKSTR 1/D-55101 MAINZ//GERMANY/ (REPRINT); UNIV MAINZ,MED KLIN 3, DEPT HEMATOL/D-55101 MAINZ//GERMANY/
Journal: JOURNAL OF MOLECULAR MEDICINE-JMM, 1998, V76, N1 (JAN), P32-47 ISSN: 0946-2716 Publication date: 19980100
Publisher: SPRINGER VERLAG, 175 FIFTH AVE, NEW YORK, NY 10010 Language: English Document Type: REVIEW
Abstract: The disappointing clinical results of cancer immunotherapy of the past few decades have not diminished the optimism about the potential of the new generation of immunotherapeutic strategies towards treatment of malignant disease. Tremendous progress has been made over recent years in unveiling the molecular basis of antigen presentation and recognition by cytotoxic T lymphocytes (CTL). The molecular concepts that have emerged from these studies have led to the design of novel anticancer vaccines and CTL-based immunotherapeutics. This review is to highlight the current molecular insights of antigen presentation and CTL recognition/activation, and their impact on the rational design of therapeutic interventions that may result in protective, CTL-based antitumor immunity.

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DIALOG(R)File 34:SciSearch(R) Cited Ref Sci
(c) 1998 Inst for Sci Info. All rts. reserv.

06343636 Genuine Article#: YK969 Number of References: 39 Title: In vitro immunization and expansion of antigen-specific cytotoxic T lymphocytes for adoptive immunotherapy using peptide-pulsed dendritic cells
Author(s): Tsai V; Kawashima I; Keogh E; Daly K; Sette A; Celis E (REPRINT)
Corporate Source: CYTEL CORP,3525 JOHN HOPKINS COURT/SAN DIEGO//CA/92121 (REPRINT); CYTEL CORP,/SAN DIEGO//CA/92121; TAKARA SHUZO CO LTD,BIOTECHNOL RES LABS/OTSU/SHIGA 52021/JAPAN/
Journal: CRITICAL REVIEWS IN IMMUNOLOGY, 1998, V18, N1-2, P65-75 ISSN: 1040-8401 Publication date: 19980000
Publisher: BEGELL HOUSE INC, 79 MADISON AVE, SUITE 1205, NEW YORK, NY 10016-7892
Language: English Document Type: ARTICLE
Abstract: The design of an effective procedure to sensitize and expand antigen-specific cytotoxic T lymphocytes (CTL) in vitro is essential for the development of effective adoptive cellular immunotherapy protocols for cancer. We have analyzed the capacity of tissue culture-derived dendritic cells (DC) to present specific peptide epitopes to CTL precursors. Our results demonstrate that peptide-pulsed DC were efficient in generating CTL responses specific for various viral and tumor epitopes, Furthermore, IL-7 and IL-10 potentiated the ability of the peptide-pulsed DC to trigger antigen-specific CTL responses. The CTL generated using this procedure efficiently recognized the naturally processed antigens and could be expanded approximately 100- to 1000-fold in tissue culture in 10 to 15 days without a loss of activity and specificity. The results and procedures described herein may facilitate the development of effective CTL-based adoptive immunotherapy for chronic viral diseases and cancer.

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DIALOG(R)File 34:SciSearch(R) Cited Ref Sci
(c) 1998 Inst for Sci Info. All rts. reserv.

06162320 Genuine Article#: XY969 Number of References: 35 Title: Transfection of IL-2 augments CTL response to human melanoma cells in vitro: Immunological characterization of a melanoma vaccine Author(s): vanElsas A; Aarnoudse C; vanderMinne CE; vanderSpek CW; Brouwenstijn N; Osanto S; Schrier PI (REPRINT)
Corporate Source: UNIV LEIDEN HOSP,DEPT CLIN ONCOL, POB 9600/NL-2300 RC LEIDEN//NETHERLANDS/ (REPRINT); UNIV LEIDEN HOSP,DEPT CLIN ONCOL/NL-2300 RC LEIDEN//NETHERLANDS/
Journal: JOURNAL OF IMMUNOTHERAPY, 1997, V20, N5 (SEP), P343-353 ISSN: 1053-8550 Publication date: 19970900
Publisher: LIPPINCOTT-RAVEN PUBL, 227 EAST WASHINGTON SQ, PHILADELPHIA, PA 19106

Language: English Document Type: ARTICLE
Abstract: We have transfected human melanoma cell line 518A2 with the cDNA encoding interleukin-2 (IL-2) or granulocyte-macrophage colony-stimulating factor (%%%GM%%%-%%%CSF%%%), and compared cytokine-producing clones for their ability to induce melanoma-specific cytotoxic T lymphocytes (CTL) from autologous peripheral blood mononuclear cells (PBMC) in vitro. The parental cell line expressed HLA-AI, HLA-A2, ICAM-1, LFA-S, in addition to the common CT, antigens MAGE-1, %%%MAGE%%%-%%%3%%%, tyrosinase, gp100, and Melan-A/MART-1. Stimulation of autologous PBMC responders with the IL-2-transfected clone 518/IL2.14 specifically induced CTL lines reactive with all cell lines derived from the autologous patient. Strikingly, %%%GM%%%- %%%CSF%%%-transfected 518A2 cells did not induce anti-tumor CTL reactivity. CTL induction against 518/IL2.14 was independent of HLA class II expression or CD4 help. The parental cell line 518A2 gained immunogenic properties when high concentrations of IL-2 were supplied exogenously, indicating that IL-2 produced and present at high levels locally by itself enhanced immunogenicity. From the autologous CTL line reactive with 518/IL2.14, clones were generated against an as yet unknown antigen, which was present in all autologous melanoma cell lines as well as in 7 of 15 HLA-A2(+) melanoma cell lines tested, but not in melanocytes. These results will be discussed with respect to the possibility of using IL-2-transfected melanoma cells as a vaccine for treatment of patients with melanoma.

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DIALOG(R)File 34:SciSearch(R) Cited Ref Sci
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06069304 Genuine Article#: BJ40F Number of References: 129 Title: Dendritic cell based therapy of cancer
Author(s): Lotze MT (REPRINT) ; Shurin M; Davis I; Amoscato A; Storkus WJ Corporate Source: UNIV PITTSBURGH,DEPT SURG, SCH MED, 300 KAUFMANN BLDG, 3471 5TH AVE/PITTSBURGH//PA/15213 (REPRINT)
, 1997, V417, P551-569
ISSN: 0065-2598 Publication date: 19970000
Publisher: PLENUM PRESS DIV PLENUM PUBLISHING CORP, 233 SPRING ST, NEW YORK, NY 10013ADVANCES IN EXPERIMENTAL MEDICINE AND BIOLOGY Series: ADVANCES IN EXPERIMENTAL MEDICINE AND BIOLOGY
Language: English Document Type: REVIEW

1/3,AB/5
DIALOG(R)File 34:SciSearch(R) Cited Ref Sci
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06051505 Genuine Article#: XR802 Number of References: 58 Title: Functional heterogeneity of HLA-A*02 subtypes revealed by presentation of a %%%MAGE%%%-%%%3%%%-encoded peptide to cytotoxic T cell clones
Author(s): Fleischhauer K (REPRINT) ; Tanzarella S; Russo V; Sensi ML; vanderBruggen P; Bordignon C; Traversari C Corporate Source: SAN RAFFAELE SCI INST,DIBIT, TELETHON INST GENE THERAPY, VIA OLGETTINA 58/I-20132 MILAN//ITALY/ (REPRINT); SAN RAFFAELE SCI INST,GENE THERAPY PROGRAM/I-20132 MILAN//ITALY/; LUDWIG INST CANC RES,/BRUSSELS//BELGIUM/; IST NAZL TUMORI,/I-20133 MILAN//ITALY/ Journal: JOURNAL OF IMMUNOLOGY, 1997, V159, N5 (SEP 1), P2513-2521
ISSN: 0022-1767 Publication date: 19970901
Publisher: AMER ASSOC IMMUNOLOGISTS, 9650 ROCKVILLE PIKE, BETHESDA, MD 20814
Language: English Document Type: ARTICLE
Abstract: The peptide-binding and presentation characteristics of seven naturally occurring HLG-A2 subtypes were studied using M3(271), a peptide derived from the tumor-specific Ag encoded by gene %%%MAGE%%%- %%%3%%%, which has been shown to be processed and presented by A*0201(+) melanoma lines, Three independent M3(271)-specific CTL clones were obtained from two unrelated A*0201(+) donors. B lymphoblastoid cell lines (BLCLs) expressing A*0201, A*0207, or A*0209 could be sensitized to lysis by all three clones upon incubation with the relevant peptide, Furthermore, the same BLCLs were able to present endogenous M3(271) in IFN-gamma release assays, These findings demonstrate, for the first time, the existence of a functional overlap between A*0207 and other A*02 subtypes, One of the CTL clones also lysed M3(271)-pulsed BLCLs expressing A*0204 and A*0206, while the other two clones recognized M3(271) only in the context of either of these two subtypes, Peptide-pulsed BLCLs expressing A*0202 or A*0205 were not lysed, although A*0205 and, with lower affinity, A*0202 molecules were shown to bind peptide M3(271), These findings have implications for the selection of cancer patients for specific immunotherapy with peptide M3(271).

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DIALOG(R)File 34:SciSearch(R) Cited Ref Sci
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05257476 Genuine Article#: VL189 Number of References: 57 Title: INDUCTION OF ANTIGEN-SPECIFIC TUMOR-IMMUNITY BY GENETIC AND CELLULAR VACCINES AGAINST MAGE - ENHANCED TUMOR PROTECTION BY COEXPRESSION OF GRANULOCYTE-MACROPHAGE COLONY-STIMULATING FACTOR AND B7-1 Author(s): BUELER H; MULLIGAN RC Corporate Source: CHILDRENS HOSP,HOWARD HUGHES MED INST,300 LONGWOOD AVE/BOSTON//MA/02115; CHILDRENS HOSP,HOWARD HUGHES MED INST/BOSTON//MA/02115; HARVARD UNIV,SCH MED,DEPT GENET/BOSTON//MA/02115 Journal: MOLECULAR MEDICINE, 1996, V2, N5 (SEP), P545-555
ISSN: 1076-1551
Language: ENGLISH Document Type: ARTICLE
Abstract: Background: A number of tumors express antigens that are recognized by specific cytotoxic T cells. The normal host immune responses, however, are not usually sufficient to cause tumor rejection. Using appropriate immunization strategies, tumor-specific antigens may serve as targets against which tumor-destructive immune responses can be generated. MAGE-1 and %%%MAGE%%%-%%%3%%% are two clinically relevant antigens expressed in many human melanomas and other tumors, but not in normal tissues, except testis. Here, we have investigated whether DNA and cellular vaccines against MAGE-1 and %%%MAGE%%%-%%%3%%% can induce antigen-specific anti-tumor immunity and cause rejection of MAGE-expressing tumors.

Materials and Methods: Mice were immunized against MAGE-1 and %%%MAGE%%%-%%%3%%% by subcutaneous injection of genetically modified embryonic fibroblasts or intramuscular injection of purified DNA. Mice were injected with lethal doses of B16 melanoma cells

expressing the corresponding MAGE antigens or the unrelated protein SIV tat, and tumor development and survival were monitored.

Results: Intramuscular expression of MAGE-1 and %%%MAGE%%%-%%%3%%% by plasmid DNA injection and subcutaneous immunization with syngeneic mouse embryonic fibroblasts transduced with recombinant retroviruses to express these antigens induced specific immunity against tumors expressing MAGE-1 and %%%MAGE%%%-%%%3%%%. Both CD4(+) and CD8(+) T cells were required for anti-tumor immunity. Coexpression of granulocyte-macrophage colony-stimulating factor (GM-CSP) or B7-1 significantly increased anti-tumor immunity in an antigen-specific manner and resulted in a considerable proportion of mice surviving lethal tumor challenge.

Conclusions: Our results suggest that genetic and cellular vaccines against MAGE and other tumor antigens may be useful for the therapy of tumors expressing specific markers, and that %%%GM%%%-%%%CSF%%% and B7-1 are potent stimulators for the induction of antigen-specific tumor immunity.
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$15.00 6 Types
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$64.40 Estimated total session cost 7.257 DialUnits
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